Module 6th

1. peptic ulcer

An “ulcer” is an open sore. The word “peptic” means that the cause of the problem is due to acid. Most of the time when a gastroenterologist is referring to an “ulcer” the doctor means a peptic ulcer.

The two most common types of peptic ulcer are called “gastric ulcers” and “duodenal ulcers”. These names refer to the location where the ulcer is found. Gastric ulcers are located in the stomach (see Figure 1). Duodenal ulcers are found at the beginning of the small intestine (also called the small bowel) known as the duodenum. A person may have both gastric and duodenal ulcers at the same time.

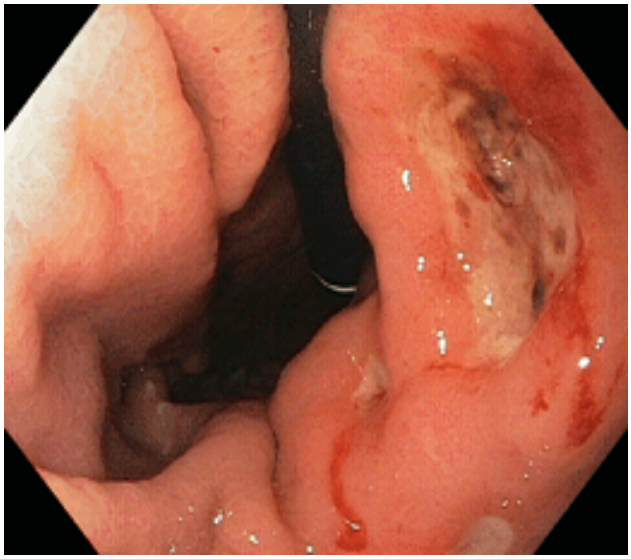

Figure 1. Photograph of a peptic ulcer taken during an upper endoscopy. This ulcer is a “gastric ulcer” because it is located in the stomach.

Symptoms

Many people with ulcers have no symptoms at all. Some people with an ulcer have belly pain. This pain is often in the upper abdomen. Sometimes food makes the pain better, and sometimes it makes it worse. Other symptoms include nausea, vomiting, or feeling bloated or full. It is important to know that there are many causes of abdominal pain, so not all pain in the abdomen is an “ulcer”.

The most important symptoms that ulcers cause are related to bleeding.

Bleeding from an ulcer can be slow and go unnoticed or can cause life-threatening hemorrhage. Ulcers that bleed slowly might not produce the symptoms until the person becomes anemic. Symptoms of anemia include fatigue, shortness of breath with exercise and pale skin color.

Bleeding that occurs more rapidly might show up as melena – jet black, very sticky stool (often compared to "roof tar") – or even a large amount of dark red or maroon blood in the stool. People with bleeding ulcers may also vomit. This vomit may be red blood or may look like "coffee grounds". Other symptoms might include "passing out" or feeling lightheaded. Symptoms of rapid bleeding represent a medical emergency. If this occurs, immediate medical attention is needed. People with these symptoms should dial 911 or go to the nearest emergency room.

Causes/Risk Factors

The two most important causes of ulcers are infection with *Helicobacter pylori* and a group of medications known as NSAIDs.

Helicobacter pylori (also called *H. pylori* or "HP) is a bacterium that lives in the stomach of infected people. The understanding that *H. pylori* can cause ulcers was one of the most important medical discoveries of the late 20th century. In fact, Dr. Barry Marshall and Dr. J. Robin Warren were awarded the 2005 Nobel Prize in Medicine for this discovery.

People infected with *H. pylori* are at increased risk of developing peptic ulcers. When a person is diagnosed with an ulcer, testing for *H. pylori* is often done. There are a number of tests to diagnose *H. pylori* and the type of test used depends on the situation.

People with ulcers. who are infected with *H. pylori.* should have their infection treated. Treatment usually consists of taking either three or four drugs. The drug therapy will use acid suppression therapy with a proton pump inhibitor (PPI) along with antibiotic therapy and perhaps a bismuth containing agent such as Pepto-Bismol. *H. pylori* can be very difficult to cure; so it is very important that people being treated for this infection take their entire course of antibiotics as prescribed.

NSAIDs (Non-Steroidal Anti-Inflammatory Drugs) are a group of medications typically used to treat pain. There are many drugs in this group. A few of these include: aspirin (Bayer®), ibuprofen (Motrin®, Advil®), naproxen (Aleve®, Naprosyn®), ketorolac (Toradol®) and oxaprozin (Daypro®). NSAIDs are also included in some combination medications, such as Alka-Seltzer®, Goody's Powder® and BC Powder®.

Acetaminophen (Tylenol®) is NOT an NSAID and is therefore the preferred non-prescription treatment for pain in patients at risk for peptic ulcer disease.

NSAID use is very common because many are available over the counter without a prescriptionand therefore they are a very common cause of peptic ulcers. NSAIDs cause ulcers by interrupting the natural ability of the stomach and the duodenum to protect themselves from stomach acid. NSAIDs also can interfere with blood clotting, which has obvious importance when ulcers bleed.

People who take NSAIDs for a long time and/or at high doses, have a higher risk of developing ulcers. These people should discuss the various options for preventing ulcers with their physician. Some people are given an acid suppressing PPI. These drugs can prevent or significantly reduce the risk of an ulcer being caused by NSAIDs.

There are many myths about peptic ulcers. Ulcers are not caused by emotional "stress" or by worrying. They are not caused by spicy foods or a rich diet. Certain foods might irritate an ulcer that is already there, however, the food is not the cause of the ulcer. People diagnosed with ulcers do not need to follow a specific diet. The days of ulcer patients surviving on a bland diet are a thing of the past.

Diagnosis

The most typical way for ulcers to be diagnosed is by a procedure called an EGD. EGD stands for EsophagoGastroDuodenoscopy. An EGD (also called "upper endoscopy") is performed by inserting a special lighted camera on a flexible tube into the person's mouth to look directly into the stomach and the beginning of the small bowel. This flexible camera carefully inspects the most likely areas for ulcers to be located. Ulcers identified during an EGD may be photographed, biopsied and even treated, if bleeding is present.

Another way ulcers were diagnosed in the past was with an x-ray test called an "upper GI series". An upper GI series involves drinking a white chalky substance called barium, and then taking a number of x-rays to look at the lining of the stomach. Doctors can see the ulcers on the x-rays when they have barium in them.

Today, the preferred method for diagnosing ulcers is with an EGD given the flexible camera is better able to detect even small ulcers and because it allows for potential treatment at that time if the ulcer is bleeding. An upper GI series can miss small ulcers and also does not allow direct treatment of an ulcer.

Treatment

The way that ulcers are treated depends on a number of features. Nearly all peptic ulcers will be treated with a proton pump inhibitor (PPI). PPIs are powerful acid blocking drugs that can be taken as a pill or given in an IV. Often, the potent IV form is used if a patient is hospitalized with a bleeding ulcer. There are six PPIs available in the United States. These are omeprazole (Prilosec®, Zegerid®), lansoprazole (Prevacid®), pantoprazole (Protonix®), rabeprazole

(Aciphex®), esomeprazole (Nexium®), and dexlansoprazole (Dexilant®). There are very few medical differences between these drugs.

PPIs require a meal to activate them. Patients should eat a meal within 30 minutes to 1 hour after taking this medication for the acid suppression therapy to work most effectively. Waiting later than this time can decrease the positive effect of this medication. This might delay healing or even result in the failure of the ulcer to heal.

Sometimes duodenal ulcers (not gastric ulcers) will be treated with H2 blockers. H2 blockers are another type of acid reducing medication. Common H2 blockers are ranitidine (Zantac®), cimetidine (Tagamet®), famotidine (Pepcid®) and nizatidine (Axid®).

An important part in treating ulcers is by identifying what caused them Patients with ulcers caused by NSAIDs should talk to their doctor about other medications that can be used to treat pain.

If the person is infected with *H. pylori* this infection should be treated. Completing the full dose of antibiotics is very important. Just as important, is making sure that the infection is gone. There are number of ways to do this. Generally, a blood test is not a good way to test if the infection is gone. The doctor who treated the infection can recommend the best way to do the "test of cure".

When someone has an ulcer that has bled significantly, treatment might be done at the time of EGD. There are a number of techniques that can be performed during an EGD to control bleeding from an ulcer. The gastroenterologist might inject medications, use a catheter to cauterize the ulcer (burn a bleeding vessel shut) or place a small clip to clamp off a bleeding vessel. Not all ulcers need to be treated this way. The doctor doing the EGD will decide if treatment is indicated based on the way the ulcer looks. The doctor will usually treat an ulcer that is actually bleeding when it is seen and will also often treat other ulcers if they have a certain appearance. These findings are sometimes called "stigmata of recent hemorrhage" or just "stigmata". Stigmata will usually get treated during the EGD if they are classified as high-risk. Common high-risk findings include a "visible vessel" and an "adherent clot".

Most ulcers can be treated and will heal. Often, people with ulcers will have to take PPIs for several weeks to heal an ulcer. It is also important to correct what caused the ulcer. When possible, NSAIDs should be stopped. Patients with ulcers caused by NSAIDs should talk to their doctor about other medications that can be used to treat pain.

If the person is infected with *H. pylori*, then completing the full dose of antibiotics is very important. Just as important, is making sure that the infection is gone. There are number of ways to do this. Generally, a blood test is not a good way to test if the infection is gone. The doctor who treated the infection can recommend the best way to do the "test of cure".

People with gastric ulcers (only in the stomach) usually have another EGD several weeks after treatment to make sure that the ulcer is gone. This is because a very small number of gastric

ulcers might contain cancer. Duodenal ulcers (at the beginning of the small intestine) usually don't need to be looked at again.

2.Ulcerative colitis

There are two forms of idiopathic inflammatory bowel disease (IBD):

(a) ulcerative colitis, a mucosal inflammatory condition confined to the rectum and colon; and (b) Crohn's disease, a transmural inflammation of the gastrointestinal tract that can affect any part, from the mouth to the anus. The etiologies of both conditions are unknown, but they may have some common pathogenetic mechanisms.

The incidence of ulcerative colitis has remained relatively constant over many years. Although most epidemiologic studies combine ulcerative proctitis with ulcerative colitis, from 17% to 49% of cases are proctitis.

Both sexes are affected equally with inflammatory bowel disease, although some studies show slightly greater numbers of women with Crohn's disease and males with ulcerative colitis.6,7 Ulcerative colitis and Crohn's disease have bimodal distributions in age of initial presentation. The peak incidence occurs in the second or third decades of life, with a second peak occurring between 50 and 80 years of age.4 A significantly increased incidence of ulcerative colitis (four to five times normal) has been observed in Ashkenazi Jews, while blacks and Asians have a relatively low incidence of occurrence.

Proposed Etiologies for Inflammatory Bowel Disease

Infectious agents
Viruses (e.g., measles)
L-Forms of bacteria
Mycobacteria
Chlamydia
Genetics
Metabolic defects
Connective tissue disorders
Environmental Factors
Diet
Smoking (Crohn's disease)
Immune defects
Altered host suceptibility
Immune-mediated mucosal damage
Psychologic factors
Stress
Emotional or physical trauma
Occupation

Although the exact etiology of ulcerative colitis and Crohn's disease is unknown, similar factors are believed responsible for both conditions. The major theories of the cause of IBD involve a combination of infectious, genetic, and immunologic factors. the inflammatory response with IBD may indicate abnormal regulation of the normal immune response or an autoimmune reaction to self-antigens. The microflora of the gastrointestinal tract may provide an environmental trigger to activate inflammation. Crohn's disease has been described as "a

disorder mediated by T lymphocytes which arises in genetically susceptible individuals as a result of a breakdown in the regulatory constraints on mucosal immune responses to enteric bacteria.

INFECTIOUS FACTORS

Microorganisms are a likely factor in the initiation of inflammation in IBD. However, no definitive infectious cause of IBD has been found, even though the presentation is similar to that caused by some invasive microbial pathogens. Patients with inflammatory bowel diseases have increased numbers of surface-adherent and intracellular bacteria. IBD may involve a loss of tolerance toward normal bacterial flora. Suspect infectious agents include the measles virus, protozoans, mycobacteria, and other bacteria. Also, certain strains of bacteria produce toxins (necrotoxins, hemolysins, and enterotoxins) that cause mucosal damage. Bacteria elaborate peptides (e.g., formyl-methionylleucyl- phenylalanine) that have chemotactic properties and that cause an influx of inflammatory cells with subsequent release of inflammatory mediators and tissue destruction. Microbes may elaborate superantigens, which are capable of global T-lymphocyte stimulation and subsequent inflammatory response. Through luminal exposure to potent nonspecific stimulatory bacterial products, the state of activation of the immune system pathways may be upregulated. As many as 70% of patients with Crohn's disease have circulating antibody to *Saccharomyces cerevisiae*, but this may not be a disease mechanism.

GENETIC FACTORS

Genetic factors predispose patients to inflammatory bowel diseases, particularly Crohn's disease. In studies of monozygotic twins, there has been a high concordance rate, with both individuals of the pair having an IBD (particularly Crohn's disease). Also, first-degree relatives of patients with IBD had a 13-fold increase in the risk of disease. Other investigators have observed genetic markers that are found more frequently in those with IBD (particularly major histocompatability complex, HLA-DR2 for ulcerative colitis and HLA-A2 for Crohn's disease). Multiple genes have been associated with IBDs; however, the nature of the gene products has not been established.

IMMUNOLOGIC MECHANISMS

The immunologic basis of IBD is supported by a number of observations. First is the pathology of the lesions. With Crohn's disease, the bowel wall is infiltrated with lymphocytes, plasma cells, mast cells, macrophages, and neutrophils. Similar infiltration has been observed in the mucosal layer of the colon in patients with ulcerative colitis. Inflammation in IBDs is maintained by an influx of leukocytes from the vascular system into sites of active disease. This influx is promoted by expression of adhesion molecules (such as alpha-4 integrins) on the surface of endothelial cells in the microvasculature in the area of inflammation.Second, many of the systemic manifestations of IBD have an immunologic etiology (e.g., arthritis or uveitis). Finally, IBD is responsive to immunosuppressive drugs (e.g., corticosteroids and azathioprine). The immune theory of IBD assumes that IBD is caused by an inappropriate reaction of the immune system. This may involve an immunodeficiency, such as a defect in cell-mediated immunity or of macrophages or neutrophils. Autoimmunity may be involved. Also, oxidant injury in colon epithelial crypt cells can be demonstrated from inflamed mucosa of patients with IBD. Potential immunologic mechanisms include both autoimmune and nonautoimmune phenomena. Autoimmunity may be directed against mucosal epithelial cells or against neutrophil cytoplasmic elements. Some patients with IBD have abnormal structural features for colonic epithelial cells even in the absence of active disease. Autoantibodies to these structures have been reported. Also, antineutrophil cytoplasmic antibodies are found in a high percentage of patients with

ulcerative colitis (70%) and much less frequently with Crohn's disease. Presence of antineutrophil cytoplasmic antibodies in left-sided ulcerative colitis is associated with resistance to medical therapy. Dysregulation of cytokines is a component of IBD. Specifically, Th1 cytokine activity (which enhances cellmediated immunity and suppresses humoral immunity) is excessive with Crohn's disease, whereas Th2 cytokine activity (which inhibits cell-mediated immunity and enhances humoral immunity) is excessive with ulcerative colitis. The result is that patients have inappropriate T-cell responses to antigens from their own intestinal microflora.19 Expression of interferon-γ (a Th1 cytokine) in intestinal mucosa of diseased patients is increased, while interleukin-4 (a Th2 cytokine) is reduced.

Tumor necrosis factor-α (TNF-α) is a pivotal proinflammatory cytokine in Crohn's disease. TNF-α can recruit inflammatory cells to inflamed tissues, activate coagulation, and promote the formation of granulomas. Production of TNF-α is increased in the mucosa and neutrophil chemoattractant. These findings have led to the consideration of leukotriene inhibitor strategies for therapy.

PSYCHOLOGICAL FACTORS

Mental health changes appear to correlate with remissions and exacerbations, especially of ulcerative colitis, but psychological factors overall are not thought to be an etiologic factor. There is a weak association between the number of stressful events experienced and the time to relapse of ulcerative colitis.

DIET, SMOKING, AND NSAID USE

Changes in diet by people in industrialized countries where Crohn's disease is more common have not been consistently associated with the disease. Studies of increased intake of refined sugars or chemical food additives and reduced fiber intake have provided conflicting results regarding risk for Crohn's disease. Smoking plays an important but contrasting role in ulcerative colitis and Crohn's disease. Smoking is protective for ulcerative colitis. The risk of developing ulcerative colitis in smokers is about 40% of that in nonsmokers. Clinical relapses are associated with smoking cessation, and nicotine transdermal administration has been effective in improving symptoms in patients with ulcerative colitis. In contrast, smoking is associated with a twofold increased frequency of Crohn's disease. Crohn's disease patients who stop smoking have a more benign course than patients who continue smoking. The mechanisms of these differing effects have not been identified. Use of nonsteroidal anti-inflammatory drugs (NSAIDs) can trigger disease occurrence or lead to disease flares.The effect of NSAIDs to inhibit prostaglandin production through cyclooxygenase inhibition may impair mucosal barrier protective mechanisms. The increased risk seems to be present for cyclooxygenase-2 inhibitors as well as cyclooxygenase-1 inhibitors.

PATHOPHYSILOGY

Ulcerative colitis and Crohn's disease differ in two general respects: anatomic sites and depth of involvement within the bowel wall. There is, however, overlap between the two conditions, with a small fraction of patients showing features of both diseases. Confusion can occur, particularly when the inflammatory process is limited to the colon.Table compares pathologic and clinical findings of the two diseases.

ULCERATIVE COLITIS

Ulcerative colitis is confined to the rectum and colon, and affects the mucosa and the submucosa. In some instances, a short segment of terminal ileum may be inflamed; this is referred to as *backwash ileitis.* Unlike Crohn's disease, the deeper longitudinal muscular layers, serosa, and regional lymph nodes are not usually involved.6 Fistulas, perforation, or obstruction

are uncommon because inflammation is usually confined to the mucosa and submucosa. The primary lesion of ulcerative colitis occurs in the crypts of the mucosa (crypts of Lieberkuhn) in the form of a crypt abscess. Here, frank necrosis of the epithelium occurs; it is usually visible only with microscopy, but may be seen grossly when coalescence of ulcers occurs. Extension and coalescence ulcers may surround areas of uninvolved mucosa. These islands of mucosa are called *pseudopolyps*.

Other typical ulceration patterns include a "collar-button ulcer," which results from extensive submucosal undermining at the ulcer edge. The extensive mucosal damage seen in ulcerative colitis can result in significant diarrhea and bleeding, although a small percentage of patients experience constipation.

Ulcerative colitis can be accompanied by complications that may be local (involving the colon or rectum) or systemic (not directly associated with the colon). With either type the complications may be mild, serious, or even life threatening. Local complications occur in the majority of ulcerative colitis patients. Relatively minor complications include hemorrhoids, anal fissures, or perirectal abscesses, and are more likely to be present during active colitis.
Enteroenteric fistulas are rare.
A major complication is toxic megacolon, which is a segmental or total colonic distension of >6 cm with acute colitis and signs of systemic toxicity. It is a severe condition that occurs in up to 7.9% of ulcerative colitis patients admitted to hospitals and results in death rates up to 50%.With toxic megacolon, ulceration extends below the submucosa, sometimes even reaching the serosa. Vasculitis, swelling of the vascular endothelium and thrombosis of small arteries occurs;
involvement of the muscularis propria causes loss of colonic tone, which leads to dilatation and potential perforation. The patient with toxic megacolon usually has a high fever, tachycardia, distended abdomen, and elevated white blood cell count, and a dilated colon is observed on x-ray. Colonic perforation, however, may occur with or without toxic megacolon and is a greater risk with the first attack. Another infrequent major local complication is massive colonic hemorrhage. Colonic stricture, sometimes with clinical obstruction, may also complicate long-standing ulcerative colitis. The risk of colonic carcinoma is much greater in patients with ulcerative colitis as compared to the general population. The risk of colon cancer begins to increase 10 to 15 years after the diagnosis of ulcerative colitis. The absolute risk may be as high as 30% 35 years after diagnosis, and as high as 49% for patients who have a long history of disease and who were less than 15 years of age at the time of diagnosis.

TREATMENT

DESIRED OUTCOME

To treat IBD properly, the clinician must have a clear concept of realistic therapeutic goals for each patient. These goals may relate to resolution of acute inflammatory processes, resolution of attendant complications (e.g., fistulas and abscesses), alleviation of systemic manifestations (e.g., arthritis), and maintenance of remission from acute inflammation, or surgical palliation or cure. The approach to the therapeutic regimen differs considerably with varying goals as well as with the two diseases, ulcerative colitis and Crohn's disease. When determining goals of therapy and selecting therapeutic regimens it is important to understand the natural history of IBD. Some cases of acute ulcerative colitis are self-limited. With mild to moderate acute colitis without systemic symptoms, 20% of patients may experience spontaneous improvement in their disease within a few weeks; however, a small percentage of patients may go on to experience more serious disease. With severe colitis, improvement without treatment cannot be expected. For

instance, the response to medical management of toxic megacolon is variable and emergent colectomy may be required. When remission of ulcerative colitis is achieved, it is likely to last at least 1 year with medical therapy. In the absence of medical therapy, one-half to two-thirds of patients are likely to relapse within 9 months.35 In some reports, remission rates with placebo have approached those found with active treatment. A considerable number of patients with active Crohn's disease may achieve at least temporary remission without drug therapy. In two large trials, 26% and 42% of ambulatory patients on placebo achieved remission. Once remission is achieved, two-thirds to three-fourths of patients remain in remission up to 2 years without drug therapy. The implication of these data is that up to 40% of patients with active Crohn's disease improve in 3 to 4 months with observation alone, and that most patients remain in remission for prolonged periods without medical intervention. These observations apply more to mild or moderate disease than to severe disease.

GENERAL APPROACH TO TREATMENT

Treatment of IBD centers on agents used to relieve the inflammatory process. Salicylates, corticosteroids, antimicrobials, and immunosuppressive agents such as azathioprine and mercaptopurine are commonly used to treat active disease, and for some agents, to lengthen the time of disease remission. In addition to the use of drugs, surgical procedures are sometimes performed when active disease is inadequately controlled or when the required drug dosages pose an unacceptable risk of adverse effects. For most patients with IBD, nutritional considerations are also important, because these patients are often malnourished. Finally, a variety of therapies may be used to address complications or symptoms of IBD. For example, antidiarrheals may be used in some patients, although these are generally to be avoided in severe ulcerative colitis because they may contribute to the development of toxic colonic dilatation. Antimicrobial agents may be used in conjunction with drainage when abscesses are present. Iron may be required, particularly with ulcerative colitis, where blood loss from the colon can be significant.

NONPHARMACOLOGIC THERAPY

NUTRITIONAL SUPPORT

Proper nutritional support is an important aspect of the treatment of patients with IBD, not because specific types of diets are useful in alleviating the inflammatory conditions, but because patients with moderate to severe disease are often malnourished either because the inflammatory process results in significant malabsorption or maldigestion, or because of the catabolic effects of the disease process. Malabsorption may occur in the patient with Crohn's disease with inflammatory involvement of the small bowel, where many nutrients are absorbed, as well as in patients who have undergone multiple small bowel resections with subsequent reduction in absorptive surface ("short gut"). Maldigestion can occur if there is a bile salt deficiency in the gut. Many specific diets have been tried to improve the condition of patients with IBD, but none has gained widespread acceptance. With each individual it is helpful to eliminate specific foods that exacerbate symptoms. This elimination process must be conducted cautiously, as patients have been known to exclude a wide range of nutritious products without adequate justification. Some patients with IBD, although not the majority, have lactase deficiency; therefore diarrhea may be associated with milk intake. In these patients, avoidance of milk or supplementation with lactase generally improves the patient's symptoms. The nutritional needs of the majority of patients can be adequately addressed with enteral supplementation.38 Patients who have severe disease may require a course of parenteral nutrition to attain a reasonable nutritional status or in preparation for surgery. In severe acute ulcerative colitis, enteral nutrition resulted in a

significantly greater increase in serum albumin, fewer adverse effects related to the nutritional regimen, and fewer postoperative infections, as compared to isocaloric, isonitrogenous parenteral nutrition.The regimens were similar with regard to remission rate and the need for colectomy. Consideration should be given to lipid administration for its caloric value, as well as in recognition of depleted peripheral fat stores in many IBD patients and the greater potential for fatty acid deficiency. Parenteral nutrition is an important component of the treatment of severe Crohn's disease or ulcerative colitis. The use of parenteral nutrition allows complete bowel rest in patients with severe ulcerative colitis, which may alter the need for proctocolectomy. Parenteral nutrition has also been valuable in Crohn's disease, because remission may be achieved with parenteral nutrition in about 50% of patients. In some patients, the disease may worsen when parenteral nutrition is stopped. Patients with enterocutaneous fistulas of various etiologies benefit from parenteral nutrition.40 Parenteral nutrition may also be valuable in children or adolescents with growth retardation associated with Crohn's disease, but surgery is often necessary with severe disease. Finally, when possible, home parenteral nutrition should be used for patients requiring long-term therapy, particularly those with "short gut" as a consequence of surgical resection. There is a growing interest in using probiotic approaches for IBD. Probiotics involves the reestablishment of normal bacterial flora within the gut by oral administration of live bacteria such as nonpathogenic *Escherichia coli*, bifidobacteria, lactobacilli, or *Streptococcus thermophilus*. Probiotic formulations have been effective in maintaining remission in ulcerative colitis.

SURGERY

Surgical procedures have an established place in the treatment of IBD. Although surgery (proctocolectomy) is curative for ulcerative colitis, this is not the case for Crohn's disease. Surgical procedures involve resection of segments of intestine that are affected, as well as correction of complications (e.g., fistulas) or drainage of abscesses. For ulcerative colitis, colectomy may be necessary when the patient has disease uncontrolled by maximum medical therapy or when there are complications of the disease such as colonic perforation, toxic dilatation (megacolon), uncontrolled colonic hemorrhage, or colonic strictures. Colectomy may be indicated in patients with longstanding disease (greater than 8 to 10 years), as a prophylactic measure against the development of cancer, and in patients with premalignant changes (severe dysplasia) on surveillance mucosal biopsies. The most common surgical procedures include proctocolectomy, after which the patient is left with a permanent ileostomy, and abdominal colectomy, with removal of the mucosa of the rectum and anastomosis of an ileal pouch to the anus (ileoanal pull-through). The risk from surgery in these patients is relatively low if the operations are performed on a nonemergent basis. The indications for surgery with Crohn's disease are not as well established as for ulcerative colitis, and surgery is usually reserved for the complications of the disease. A recognized problem with intestinal resection for Crohn's disease is the high recurrence rate. Surgery may be appropriate in well-selected patients who have severe or incapacitating disease or obstruction in spite of aggressive medical management. The surgical procedures performed include resections of the major intestinal areas of involvement. In some patients with severe rectal or perineal disease, diversion of the fecal stream is performed with a colostomy. Other indications for surgery include the finding of colon cancer, an inflammatory mass, or intestinal perforations.

PHARMACOLOGIC THERAPY

Drug therapy plays an integral part in the overall treatment of IBD. None of the drugs used for IBD is curative; at best they serve to control the disease process. Therefore a reasonable goal of

drug therapy is resolution of disease symptoms such that the patient can carry on normal daily functions. The major types of drug therapy used in IBD include aminosalicylates, corticosteroids, immunosuppressive agents (azathioprine, mercaptopurine, cyclosporine, and methotrexate), antimicrobials (metronidazole and ciprofloxacin), and agents to inhibit TNF-α (anti-TNF-α antibodies). Sulfasalazine, an agent that combines a sulfonamide (sulfapyridine) antibiotic and mesalamine (5-aminosalicylic acid) in the same molecule, has been used for many years to treat IBD butwas originally intended to treat arthritis. Sulfasalazine is cleaved by gut bacteria in the colon to sulfapyridine (which is mostly absorbed and excreted in the urine) and mesalamine (which mostly remains in the colon and is excreted in stool). The active component of sulfasalazine is mesalamine. The mechanism of action of mesalamine is not well understood. Cyclooxygenase or lipoxygenase inhibition alone do not account for the agent's effects. Aminosalicylates may block production of prostaglandins and leukotrienes, inhibit bacterial peptide-induced neutrophil chemotaxis and adenosine-induced secretion, scavenge reactive oxygen metabolites, and inhibit activation of the nuclear regulatory factor NF-κB. Because the mechanism of action of sulfasalazine is not related to the sulfapyridine component, and since sulfapyridine is believed to be responsible for many of the adverse reactions to sulfasalazine, mesalamine alone can be used. Mesalamine can be used topically as an enema for the treatment of proctitis, or given orally in slowrelease formulations that deliver mesalamine to the small intestine and colon. Slow-release oral formulations of mesalamine such as Pentasa release mesalamine from the duodenum to the ileum, with about 75% of the drug passing into the colon. Olsalazine is a dimer of two 5-aminosalicylate molecules linked by an azo bond. Mesalamine is released in the colon after colonic bacteria cleave olsalazine. Balsalazide is a mesalamine prodrug that is enzymatically cleaved in the colon to produce mesalamine. The recommended daily doses of the oral mesalamine derivatives are intended to approximate the molar equivalent of mesalamine present in 4 g of sulfasalazine. At present, sulfasalazine is used in preference to oral mesalamine derivatives, mainly because it costs much less. However, it is not tolerated as well as the mesalamine alternatives. Because the oral mesalamine formulations are coated tablets or granules, they should not be crushed or chewed. Corticosteroids and adrenocorticotropic hormone have been widely used for the treatment of ulcerative colitis and Crohn's disease, given parenterally, orally, or rectally. Corticosteroids are believed to modulate the immune system and inhibit production of cytokines and mediators. It is not clear whether the most important steroid effects are systemic or local (mucosal). Budesonide is a corticosteroid that is administered orally in a controlled-release formulation. The drug undergoes extensive first-pass metabolism, so systemic exposure is thought to be minimized. Immunosuppressive agents such as azathioprine, mercaptopurine (a metabolite of azathioprine), methotrexate, or cyclosporine are sometimes used for the treatment of IBD.

OBESITY

If the 'ideal weight' of an individual is that which maximises life expectancy, 'obesity' may be defined as an illness where the health (and hence life expectancy) is adversely affected by excess body fat.[1] But at what point does an individual become 'obese'? The generally accepted benchmark, as proposed by the World Health Organization expert committee, is the *body mass index* (*BMI*). The BMI is calculated by dividing the body mass (in kg) by the square of the height (in metres). Although it is not a perfect index (e.g. it does not distinguish between fat and lean mass), the BMI is generally well correlated with other measurements of body fat, and it is widely employed in obesity studies. While there are problems in defining a 'healthy' weight for a particular population, it is generally agreed that people with a BMI of < 18.5 kg/m^2 should be classified as 'underweight', and those with a BMI of 18.5-24.9 kg/m^2 are regarded as of 'acceptable' or 'normal' weight. A BMI in the range of 25.0-29.9 kg/m^2 signifies 'grade 1 overweight'. If the BMI is between 30.0 and 39.9 kg/m^2, the patient is deemed to be obese or 'grade 2 overweight', while those with a BMI of > 40 kg/m^2 are said to be 'grade 3 overweight' or morbidly obese.

THE HOMEOSTATIC MECHANISMS CONTROLLING ENERGY BALANCE

A common view and one that is implicitly encouraged by authors of numerous dieting books as well as the enormously lucrative dieting industry in general, is that obesity is simply the result of bad diet or wilful overeating (hyperphagia). In truth, however, the situation is more complex. Many people exposed to the same dietary choices fail to become obese, and the failure rate in such diets is high (probably 90%), with most eventually returning to their original starting weight, suggesting the operation of some intrinsic homeostatic system that strives to maintain a particular set weight. This mechanism is normally exceptionally precise, and it has been calculated that it is capable of regulating energy balance to 0.17% per decade. A truly remarkable feat considering the day-to-day variations in food intake.

Studies of obesity in monozygotic and dizygotic twins have established a strong genetic influence on the susceptibility to the disease, and studies of rare mutations in mice (and more recently in humans) have led to the discovery and elucidation of the neuroendocrine pathways that match food intake with energy expenditure, and to the concept that it is, in fact, disorders of this system that are responsible for the onset and maintenance of the disease.

THE ROLE OF LEPTIN IN BODY WEIGHT REGULATION

At the beginning of the 20th century, it was observed that patients with damage to the hypothalamus tended to gain weight. In the 1940s, it was also shown that discrete lesions in the hypothalamus of rodents caused them to become obese. As early as 1953, Kennedy proposed, on the basis of experiments on rats, that a hormone released from adipose tissue acted on the hypothalamus to regulate body fat and food intake, thus setting the stage for future discoveries in this area.

It was well established that mice can become obese as a result of mutations in certain genes. At least five of these have now been identified-including the *ob* (obesity), *tub* (tubby), *fat* and *db* (diabetes) genes. Mice that are homozygous for mutant forms of these genes-*ob/ob* mice and *db/db* mice-eat excessively and have low energy expenditure, become grossly fat, and have

numerous metabolic and other abnormalities. Weight gain in an *ob/ob* mouse is suppressed if its circulation is linked to that of a normal mouse, implying that the obesity is caused by lack of a blood-borne factor.

An important breakthrough came in 1994, when Friedman and his colleagues cloned the *ob* gene and identified its protein product-*leptin* (the word is derived from the Greek *leptos,* meaning thin). When recombinant leptin was administered to *ob/ob* mice, it strikingly reduced food intake and body weight. It had a similar effect when injected directly into the lateral or the third ventricle, implying that it acted on the regions of the brain that control food intake and energy balance. Recombinant leptin has similar effects in humans.

Leptin mRNA is expressed in adipocytes; its synthesis is increased by glucocorticoids, insulin and the oestrogens, and it is reduced by β-adrenoceptor agonists. In humans, the concentration of leptin in the circulation varies according to the fat stores and BMI in normal subjects; the release is pulsatile and inversely related to hydrocortisone levels. Leptin enters the central nervous system (CNS) by a saturable transport mechanism, in amounts proportional to the plasma level. It acts on hypothalamic nuclei that express specific leptin receptors. Insulin also plays an important part in regulating energy balance. It strongly stimulates leptin expression in fat cells. But its role as a fat sensor is more complex, and it is accepted that leptin has the more critical role.

Today, the adipocyte is regarded not only as a storage depot for fat, but also as an important staging post on the energy information highway. These cells secrete a host of other cytokines and other autocrine, paracrine and endocrine mediators, leading some authorities to consider that adipose tissue is a dispersed endocrine organ.

INTEGRATION OF INFORMATION AND EFFECT ON ENERGY BALANCE

Leptin's main targets in the hypothalamus are two groups of neurons in the *arcuate nucleus*. These have opposing actions, and energy homeostasis depends, in the first instance, on the balance between these actions. In one group, the peptides *neuropeptide Y* (*NPY*) and *agouti-related peptide* are colocalised. The other group contains the protein *prepro-opiomelanocortin* (*POMC*) and releases α-*melanocyte-stimulating hormone* (α-*MSH*), which is a proteolytic product of POMC cleavage. Both groups of neurons express specific leptin receptors.

Falling leptin levels activate the first group of neurons, resulting in increased food intake (an *orexigenic* effect), and synthesis and storage of fat (anabolism), as well as decreased energy expenditure. Conversely, rising leptin levels activate the second group of neurons, producing the opposite *anorexigenic* and catabolic effect. The signal transduction mechanisms triggered by leptin receptor activation are thought to involve the Jak/Stat pathway and activation of an ATP-sensitive potassium channel. Orexigenic neurons project into the paraventricular nucleus, and anorexigenic neurons into the lateral hypothalamic area. Interestingly, these two areas had previously been identified, using lesioning techniques, as 'hunger' and 'satiety' centres.

The integration of the information on fat stores (adiposity signals) with other nutritional information is very complex. Leptin, although apparently a crucial coordinator, is only one part

of the process. Insulin receptors also occur on both groups of hypothalamic neurons, and it is thought that leptin and insulin act in concert at this important regulatory site.

REGULATION OF FOOD INTAKE AND ENERGY EXPENDITURE

Food intake is of course modified by a multitude of physiological, psychological, financial and social factors, and so the long-term regulation of energy balance by adiposity signals such as leptin and insulin must of necessity occur against a background of day-to-day variations in meal size, frequency and content. Food intake appears to be modulated by feedback loops in which signals from the gastrointestinal tract are transmitted to the CNS, apparently converging on the *nucleus tractus solitarius*. Some of these signals arise from vagal and other spinal afferents originating in the gastrointestinal tract. Another important endocrine afferent signal is *cholecystokinin*-a peptide secreted by the duodenum in response to the process of eating and digestion of (especially fatty) foodstuffs. Cholecystokinin acts locally on cholecystokinin A receptors in the gastrointestinal tract to stimulate vagal afferents and may, in its capacity as a neurotransmitter, also act on cholecystokinin B receptors in the brain in order to function as a satiety factor. Studies in rodents show how these short-term satiety signals are integrated into the overall context of the body's energy economy by regulation of meal size. For example, the stimulation of food intake by NPY is largely attributable to larger meal sizes, whereas treatment with leptin leads to a reduction in meal size rather than frequency.

THE PATHOPHYSIOLOGY OF HUMAN OBESITY

In most adult subjects, body fat and body weight remain more or less constant over many years, even decades, in the face of very large variations in food intake and energy expenditure-amounting to about a million calories per year. The steady-state body weight and BMI of an individual is, as has been stressed above, the result of the integration of multiple interacting factors, and perturbations-either in the direction of increase or decrease-are resisted by homeostatic mechanisms. How, then, does obesity occur? Why is it so difficult for the obese to lose weight and maintain the lower weight?

The main determinant is manifestly a disturbance of the homeostatic mechanisms that control energy balance, but genetic endowment underlies this disturbance. Other factors, such as food intake and lack of physical activity, contribute, and there are, of course, social, cultural and psychological aspects. We will deal below with the imbalance of homeostatic mechanisms and genetic endowment, and then briefly mention the role of food intake and physical activity. The role of social, cultural and psychological aspects we will leave (with a profound sigh of relief) to the psychosociologists.

OBESITY AS A DISORDER OF THE HOMEOSTATIC CONTROL OF ENERGY BALANCE

Because the homeostatic control of energy balance is extremely complex, it is not easy to determine what goes wrong in obesity. When the leptin story unfolded, it was thought that

alterations in leptin kinetics might provide a simple explanation. There is a considerable interindividual variation in sensitivity to leptin, and some individuals seem to produce insufficient amounts of this hormone. Paradoxically, however, plasma leptin is often higher in obese individuals, compared with non-obese subjects, not lower as might be expected. The reason for this is that *resistance* to leptin rather than insufficient hormone is more prevalent in obesity. Such resistance could be caused by defects in leptin synthesis, in its carriage in the circulation, in its transport into the CNS, in leptin receptors in the hypothalamus (as occurs in *db/db* mice) or in postreceptor signalling. There is some evidence that the action of a member of the family of suppressors of cytokine signalling, SOCS-3, may underlie or contribute to leptin resistance.

Dysfunction of mediators other than leptin could be implicated in obesity. For example, TNF-α, another cytokine that can relay information from fat tissue to brain, is increased in the adipose tissue of insulin-resistant obese individuals. Another pathophysiological alteration in obesity is a reduced insulin sensitivity of muscle and fat, and decreased β_3 adrenoceptor function in brown adipose tissue (see above) may also occur; alternatively, UCP-2, one of the proteins that uncouple oxidative phosphorylation in adipocytes, could be dysfunctional in obese individuals.

A further suggestion is that alterations in the function of specific nuclear receptors, such as PPARα, β and γ, may play a role in obesity. These receptors regulate gene expression of enzymes associated with lipid and glucose homeostasis, and they also promote the genesis of adipose tissue. PPARγ is expressed preferentially in fat cells and synergises with another transcription factor, C/EBPα, to convert precursor cells to fat cells. The gene for UCP (see above) in white fat cells also has regulatory sites that respond to PPARα and C/EBPα. A new class of agents, the *thiazoladinediones*, bind to and activate PPARγ . One of these, **troglitazone**, is licensed in the UK for treatment of type 2 diabetes. The pathophysiology of obesity could involve disturbance(s) in any of the multitude of other factors involved in energy balance.

GENETIC FACTORS AND OBESITY

Analyses of large-scale (> 100000) studies in human monozygotic and dizygotic twin pairs indicate that 50-90% of the variance of BMI can be attributed to genetic factors, and suggest a relatively minor role for environmental factors. This conclusion may seem surprising, but feeding studies using laboratory rodents where food intake is held constant have demonstrated the importance of genetic background to body weight regulation, and this is especially true for high-fat diets. The prevailing viewpoint is that susceptibility to obesity is largely determined by genetic factors, while environmental factors determine the expression of the disease.

The discovery that spontaneous mutations arising in single genes (e.g. the *ob/ob* genotype) produced obese phenotypes in mice led to a search for equivalent genes in humans. A recent review reported over 170 human obesity cases that could be traced to single gene mutations in 10 different genes. Leptin receptor or POMC mutations are sometimes observed, but MC4R mutations, however, seem to be more prevalent (3-5%) in obese patients. In general, however, human obesity should be regarded as a polygenic disorder involving the interaction of many genes. At the time of writing, > 600 genes, markers and chromosomal regions are under

investigation for linkage to human obesity, and all information is annually updated on the Obesity Gene Map Database.

Other genes that appear to be involved include the β_3 adrenoceptor and the glucocorticoid receptor. Decreased function of the β_3 adrenoceptor gene could be associated with impairment of lipolysis in white fat or with thermogenesis in brown fat. A mutation of this gene has been found to be associated with abdominal obesity, insulin resistance and early-onset type 2 diabetes in some subjects and a markedly increased propensity to gain weight in a separate group of morbidly obese subjects. Alterations in the function of the glucocorticoid receptor could be associated with obesity through the permissive effect of glucocorticoids on several aspects of fat metabolism and energy balance.

FOOD INTAKE AND OBESITY

As Spiegelman & Flier point out, 'one need not be a rocket scientist to notice that increased food intake tends to be associated with obesity'. A typical obese subject will usually have gained 20 kg over a decade or so. This means that there has been a daily excess of energy input over output of 30-40 kcal initially, increasing gradually to maintain the increased body weight.

The type of food eaten, as well as the quantity, can disturb energy homeostasis. Fat is an energy-dense foodstuff, and it may be that the mechanisms regulating appetite react more rapidly to carbohydrate and protein than to fat-too slowly to stop an individual consuming too much high-fat food before the satiety systems come into play.

Obese individuals diet to lose weight. However, when a subject reduces calorie intake, shifts into negative energy balance and loses weight, the resting metabolic rate decreases, and there is a concomitant reduction in energy expenditure. Thus an individual who was previously obese and is now of normal weight generally needs fewer calories to maintain that weight than an individual who has never been obese. The decrease in energy expenditure appears to be largely caused by an alteration in the conversion efficiency of chemical energy to mechanical work in the skeletal muscles. This adaptation to the caloric reduction contributes to the difficulty of maintaining weight loss by diet.

PHYSICAL EXERCISE AND OBESITY

It used to be said that the only exercise effective in combating obesity was pushing one's chair back from the table. It is now recognised that physical activity-i.e. increased energy expenditure-has a much more positive role in reducing fat storage and adjusting energy balance in the obese, particularly if associated with modification of the diet. An inadvertent, natural population study provides an example. Many years ago, a tribe of Pima Indians split into two groups. One group settled in Mexico and continued to live simply at subsistence level, eating frugally and spending most of the week in hard physical labour. They are generally lean and have a low incidence of type 2 diabetes. The other group moved to the USA-an environment with easy access to calorie-rich food and less need for hard physical work. They are, on average, 57 lbs (26 kg) heavier than

the Mexican group and have a high incidence of early-onset type 2 diabetes.

PHARMACOLOGICAL APPROACHES TO THE PROBLEM OF 3.OBESITY

The first weapons in the fight against obesity are diet and exercise. Unfortunately, these often fail or show only short-term efficacy, leaving only heroic surgical techniques (such as gastric stapling or bypass) or drug therapy as a viable alternative.

Obesity

- Obesity is a multifactorial disorder of energy balance, in which long-term calorie intake exceeds energy output.
- It is characterised by an excessive body mass index (BMI; weight in kg divided by the square of height in m).
- A subject with a BMI of 20-25 kg/m^2 is considered as having a healthy body weight, one with a BMI of 25-30 kg/m^2 as overweight, and one with a BMI > 30 kg/m^2 as obese.
- Obesity is a growing problem in most rich nations; the incidence-at present approximately 30% in the USA and 15-20% in Europe-is increasing.
- A BMI > 30 kg/m^2 significantly increases the risk of type 2 diabetes, hypercholesterolaemia, hypertension, ischaemic heart disease, gallstones and some cancers.
- The causes of obesity may include:
    - deficiencies in the genesis of and/or the response to leptin or other adiposity signals
    - defects in the hypothalamic neuronal systems responding to leptin or other adiposity signals
    - defects in the systems controlling energy expenditure (e.g. reduced sympathetic activity), decreased metabolic expenditure of energy, or decreased thermogenesis caused by a reduction in β_3 adrenoceptor-mediated tone and/or dysfunction of the proteins that uncouple oxidative phosphorylation
    - an important genetic contribution.

The attempt to control appetite with drugs has had a long and largely undistinguished history. Many types of 'anorectic' (e.g. appetite suppressant) agents have been tested in the past, including the uncoupling agent **DNP**, **amphetamines** and **fenfluramine**. However, these are no longer used, and the only two drugs currently licensed in the UK for the treatment of obesity are **sibutramine** and **orlistat** . The two agents work in totally different ways, with sibutramine acting on the CNS to suppress appetite (a true anorectic effect), while orlistat acts within the gastrointestinal tract to prevent fat absorption. Neither should be given without other concomitant dietary and other therapy (e.g. exercise). As might be imagined, the quest for further

effective antiobesity agents is the subject of a prodigious effort by the pharmaceutical industry.

SIBUTRAMINE

Sibutramine, originally intended as an antidepressant, has shown promise in the treatment of obesity. The drug inhibits the reuptake of serotonin and noradrenaline at the hypothalamic sites that regulate food intake. Its main effects are to reduce food intake and cause dose-dependent weight loss, the weight loss being associated with a decrease in obesity-related risk factors. Sibutramine enhances satiety and is reported to produce a reduction in waist circumference (i.e. a reduction in visceral fat), a decrease in plasma triglycerides and very low-density lipoproteins, but an increase in high-density lipoproteins. In addition, beneficial effects on hyperinsulinaemia and the rate of glucose metabolism are said to occur. There is some evidence that the weight loss is associated with higher energy expenditure, possibly through an increase in thermogenesis mediated by the sympathetic nervous system.

A recent meta-analysis of three long-term treatment studies utilising sibutramine in comparison with placebo concluded that there was a 4.6% loss of weight after 1 year's treatment with the drug. There was also a higher (15%) increase in patients who lost more than 10% of their body mass among those taking the drug.

In the UK, the drug is licensed for use in periods up to a year, and the National Institute for Health and Clinical Excellence has advised that it should not be given to people who have not already tried conscientiously to lose weight by other means.

Pharmacokinetic aspects

Sibutramine is given orally, is well absorbed and undergoes extensive first-pass metabolism. The metabolites are responsible for the pharmacological actions. Steady-state blood levels of the metabolites occur within 4 days. The active metabolites are inactivated in the liver, and 85% of the inactive residues are excreted in the urine and faeces.

Unwanted effects

Sibutramine increases heart rate and blood pressure. Regular monitoring of these parameters is essential, and the drug is contraindicated if cardiovascular disease is present or if the systolic or diastolic pressure is raised by 10 mmHg or more. Other unwanted effects include dry mouth, constipation and insomnia. Interactions with drugs that are metabolised by one of the P450 isoenzymes can occur.

Orlistat reacts with serine residues at the active sites of gastric and pan
the enzymes and thereby preventing the breakdown of dietary fat to fat
causes a dose-related decrease in fat absorption and a corresponding in
plateaus at some 30% of dietary fat. Given with a low-calorie diet in ol
modest but consistent loss of weight compared with in placebo-treated
analysis of 11 long-term placebo-controlled trials encompassing over 6
produce a 2.9% greater reduction in body weight than in the control gr

or more of their body weight compared with the controls.

Orlistat is also reported to be effective in patients suffering from type 2 diabetes and other complications of obesity, to reduce leptin levels and blood pressure, to protect against weight loss-induced changes in biliary secretion, to delay gastric emptying and gastric secretion, to improve several important metabolic parameters, and not to interfere with the release or action of thyroid and other important hormones. It does not induce changes in energy expenditure.

Pharmacokinetic aspects

Virtually all (97%) of orlistat is excreted in the faeces (83% unchanged), with only negligible amounts of the drug or its metabolites being absorbed.

Unwanted effects

Abdominal cramps, flatus with discharge and faecal incontinence can occur, as can intestinal borborygmi (rumbling) and oily spotting. Surprisingly, in view of the possibility of these antisocial effects occurring, the drug is well tolerated. Supplementary therapy with fat-soluble vitamins may be needed, and there has been a report of decreased absorption of contraceptive pills.

No significant drug interactions have been noted, except in the case of **ciclosporin** ,where reduced absorption of the latter drug has been reported.

PSYCHOTROPIC DRUG THERAPY IN OBESITY

While they cannot be regarded as specific therapies, a common clinical finding is that some subgroups of obese patients, such as those with concomitant depression, respond well to mood-altering drugs such as the selective serotonin uptake inhibitors.

4.THYROID DISORDERS

Disorders of Parathyroid Gland