GI

MEDICAL GRAND ROUNDS

# ABSORPTION AND MALABSORPTION

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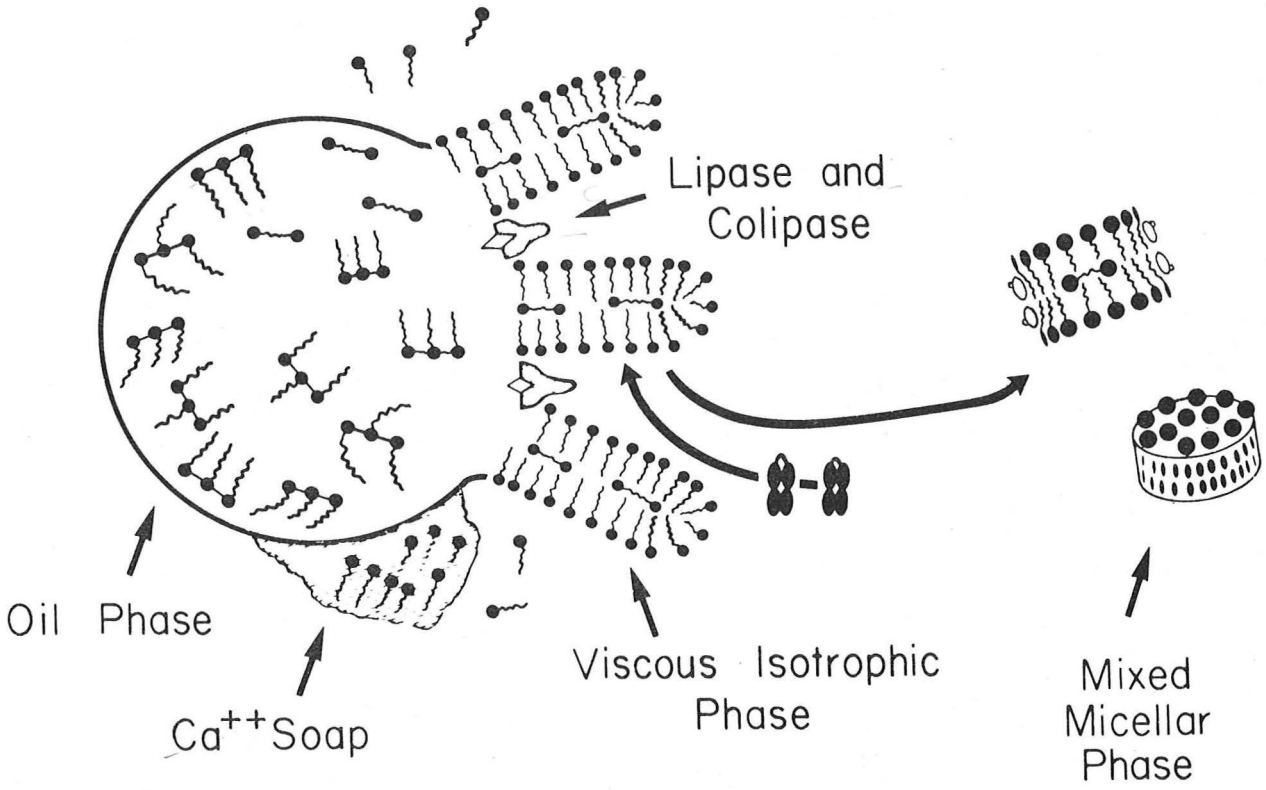


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## Section 1: INTRODUCTION

Fats, proteins, and complex carbohydrates represent the major sources of calories in the typical diet found in the Western world. During digestion within the proximal small intestine proteins and carbohydrates are broken down into simpler peptides and saccharides that are very polar and so are soluble in the aqueous environment of the intestinal contents. Because of the high degree of interaction between these hydrophilic products and the water phase, carrier-mediated and energy-linked transport processes are required to bring about net transfer of these molecules from the intestinal lumen into the cytosolic compartment of the columnar absorptive cell of the jejunum and ileum. In contrast, the digestion of complex dietary lipids releases products that are still very nonpolar and, therefore, have very low aqueous solubilities. Such molecules are, however, readily absorbed across the microvillus membrane of the intestinal cell by passive mechanisms. Failure of one or more of these absorptive mechanisms leads to what has been called the "malabsorption syndromes".

In the broadest sense, the term "malabsorption syndrome" can be construed to include almost any disease in which there is excessive loss of some constituent of the diet, including water and electrolytes, in the feces. When used in this manner, such diverse illnesses as viral gastroenteritis, the disaccharidase deficiency states, various enteric bacterial infections, diseases destroying pancreatic function, diseases of the small intestinal mucosa, and innumerable other clinical disorders may be included. Conventionally, however, the term is used in a more restricted sense, including only those diseases in which there is excessive loss of one or more major caloric sources in the feces, i.e., excessive loss of fat, protein, or carbohydrate. Since the digestion and absorption of dietary fat is more complex, and therefore more vulnerable, than the digestion and absorption of either protein or carbohydrate, nearly all these diseases manifest excessive excretion of fat in the stool, i.e., steatorrhea. For this reason, the terms malabsorption syndrome and steatorrhea syndrome are often used interchangeably. It should be emphasized, however, that although steatorrhea is the most common manifestation of this group of diseases, patients also may have excessive fecal loss of protein or carbohydrate, depending on the nature of the defect produced by the specific underlying disease.

The normal mechanisms of digestion and absorption are complex, and depend on the functional integrity of at least four major physiological systems within the body: secretion of digestive enzymes by the pancreas; maintenance of adequate concentrations of bile acids in the enterohepatic circulation; absorption of various dietary components into the intestinal mucosal cells; and delivery of these substances into either the intestinal blood capillary or lymphatic vessel. A particular disease may interfere with the absorption of fat, protein, or carbohydrate by altering the normal function of any one of these systems. Therefore, an understanding of the basic causes of the malabsorption syndrome, as well as the differential diagnostic approach to the patient with this disorder, requires a thorough understanding of the normal mechanisms of digestion and absorption.

## Section 2: DIFFERENTIAL DIAGNOSIS OF DIARRHEA

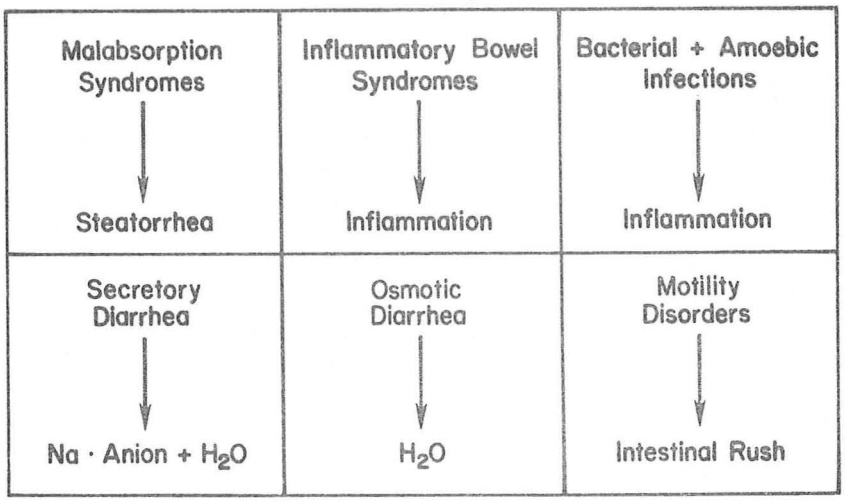
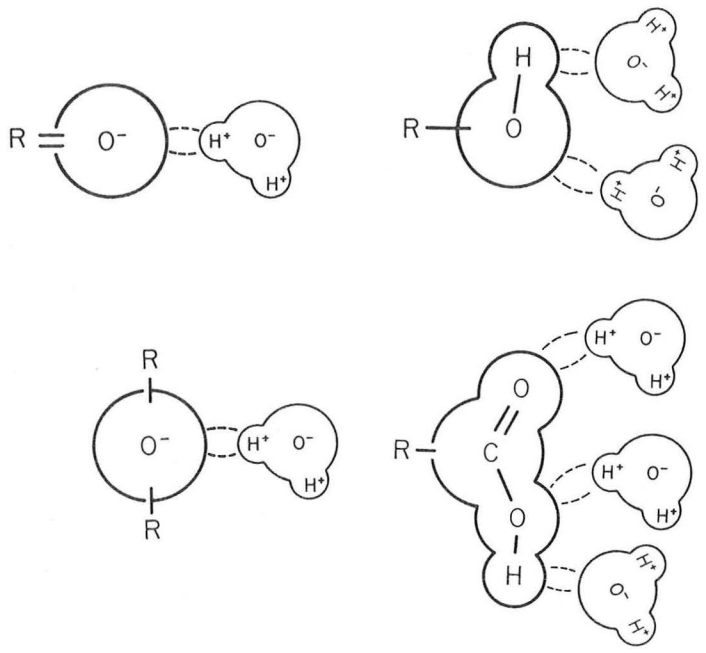



Fig. 1 summarizes the major clinical syndromes that commonly present with more serious or prolonged diarrhea that must be considered in any patient who presents to the physician or to the emergency room with the chief complaint of an increased frequency or liquidity of his/her bowel movements. The first major group of diseases are classified under the general category of malabsorption syndromes. This category includes a large number of individual illnesses all of which are characterized by failure to digest or failure to absorb at least dietary fat (in some cases dietary carbohydrate and protein also will be malabsorbed). This group of diseases include such diverse entities as pancreatic insufficiency, blindloop syndromes, sprue and obstruction of the intestinal lymphatics. This group of diseases is usually identified by performing either a qualitative or quantitative stool fat determination. The finding of excessive amounts of fat in the stool (steatorrhea) essentially identifies a patient as belonging to this category of disease. A second group of patients will present with a moderate to very large-volume, watery diarrhea. Usually, they will manifest no steatorrhea and no symptoms of systemic illness (no fever, elevation of the WBC). Such patients are generally separated into two groups depending upon whether the diarrhea is due to secretory process or due to the presence of an osmotically active material in the gut lumen. The secretory diarrhea may be due to many specific causes such as the production of substances either in the gut lumen or in the vascular space (from tumors) that induce the secretion of an isosmotic fluid. The diarrhea is often of a very large volume and persists even during fasting. The osmotic pressure of the stool water is usually fully accounted for by the content of electrolytes. Osmotic diarrhea is, on the other hand, usually produced by the presence of osmotically active molecules in the intestinal lumen that pull water from the vascular space and cause diarrhea. Such syndromes generally produce diarrhea of only moderate volumes and the diarrhea ceases with fasting. Often, there is an "osmotic gap" in that the osmotic pressure of the stool water cannot be accounted for by the concentration of sodium, potassium and appropriate anions. Finally, there is also a group of illnesses in which there appears to be a primary motility disorder. The diarrhea in these cases is presumably caused by rapid intestinal transit through the gastrointestinal tract.

In contrast to these major syndromes presenting with steatorrhea, intestinal rush or a larger volume, watery diarrhea, there are two other groups of illnesses that present primarily with evidence of colonic (and small bowel) inflammation: such patients generally fall into two categories including those who have idiopathic inflammatory bowel disease (ulcerative colitis and Crohn's disease) and individuals who have bacterial or amoebic infections of the colon. Clearly, this group of patients must be identified by finding evidence of systemic tissue invasion (fever, elevated WBC, GI bleeding, etc.) and establishing that colonic (and, occasionally small intestine) inflammation exists.

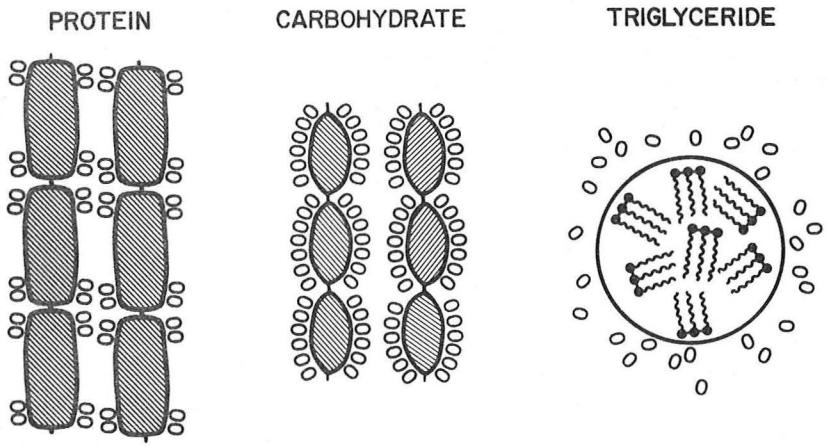
## Section 3: NORMAL MECHANISMS OF FAT, PROTEIN AND CARBOHYDRATE DIGESTION AND ABSORPTION

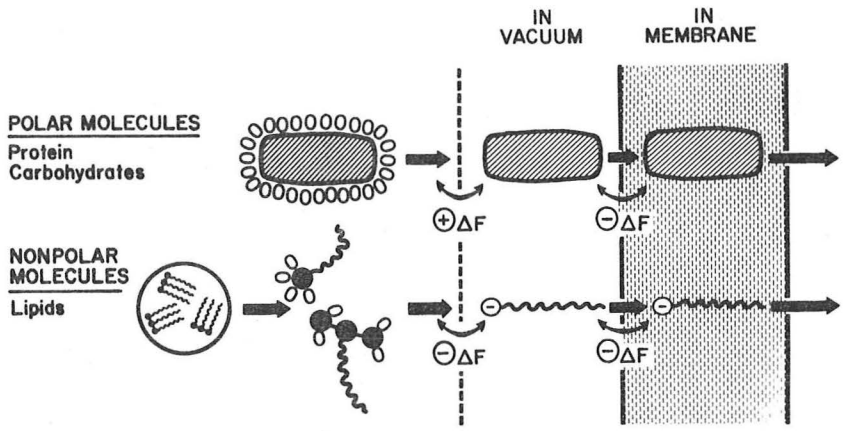
The processes of food digestion and the subsequent absorption of various products across the gastrointestinal tract takes place essentially in an environment of water. The characteristics of the digestive and transport processes that result in the absorption of nutrients are largely dictated by the thermodynamic characteristics of the interaction of water molecules with the various food substances through the process of hydrogen bonding. It has long been known that certain hydrogen-containing compounds, and particularly water, form molecular complexes with a variety of other substances. For sometime it was believed that these associations were the result of coordinate covalent linkages between strongly electronegative atoms. More recently, however, this was clearly shown not to be the case. Rather, the associations between molecules attributable to hydrogen bonding is largely ionic in character. When hydrogen becomes associated with strongly electronegative atoms such as florine, oxygen and nitrogen, electrons are shifted away from the hydrogen atom. As a consequence, in a compound such as water the portion of the molecule containing the two hydrogen atoms becomes relatively positively charged while the portion of the molecule containing the oxygen atom becomes relatively negatively charged. As a consequence, the water molecule, in effect, becomes a dipole. Such dipoles interact with one another and with other electronegative groups to form hydrogen bonds. These bonds are of relatively great strength and require, on average, 3000-4000 calories per mole to disrupt.



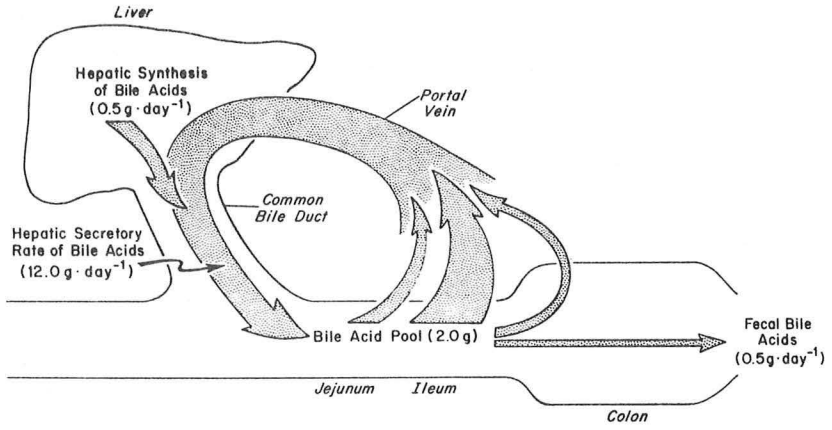
As illustrated in Fig. 2, water molecules readily interact, through hydrogen bonding, with electronegative groups on organic molecules. On average, the oxygen present in ethers, aldehydes and ester linkages form one hydrogen bond. Alcohol groups are capable of hydrogen bonding to at least two water molecules while an unionized carboxyl function forms, on average, 3 hydrogen bonds. The greater the number of hydrogen bonds that can be formed by a particular compound, the greater is its "polarity" or, more properly, its hydrophilicity.

Basically, the major components of the diet can be divided into two groups. Both protein and carbohydrate have a large number of chemical constituent groups that can undergo hydrogen bonding with water. As a consequence, these compounds (and their component amino acids and sugar) are relatively polar and water soluble. In contrast, triglyceride is essentially unable to form any hydrogen bonds with water. As a consequence, water excludes triglyceride molecules from the aqueous phase and forces them into a nonreactive, insoluble, hydrocarbon oil droplet (Fig. 3).





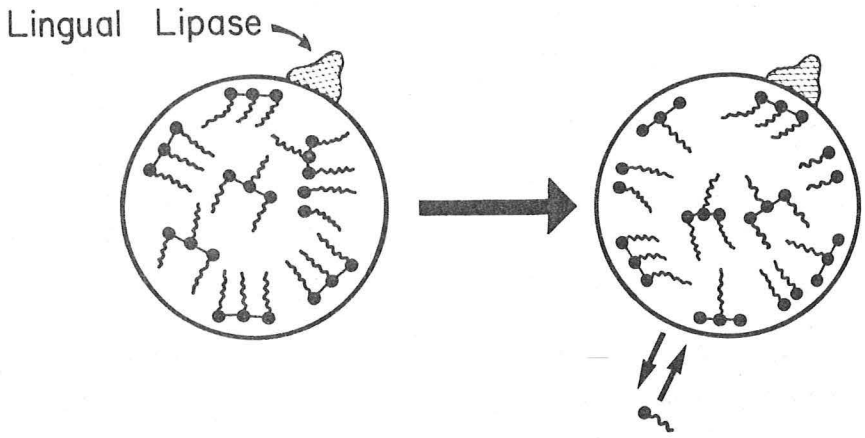

As illustrated in Fig. 4, therefore, the basic process of digestion and absorption involves two separate types of processes. In both cases the process of absorption involves, first, the disruption of all bonds between the solute and water molecules and, second, the movement of the molecule into the substance of the biological membrane. This process can be thought of as, first, the movement of the solute molecule from the water phase into a vacuum and, second, the movement of the solute from the vacuum into the membrane. In the case of polar or hydrophylilic molecules (such as sugars, amino acids, water soluble vitamins) the major energy barrier to transmembrane movement involves the breaking of all hydrogen bonds between the solute molecule and the water phase. Thus, absorption of very hydrophylilic molecules usually requires the expenditure of large amounts of energy by the membrane and is commonly associated with an energy linked carrier mechanism. Nonpolar or hydrophobic molecules such as triglyceride cannot interact at all with biological membranes. Hence, the process of digestion usually takes place during which an amphipathic molecule is produced. Such amphipaths have one portion of the molecule that interacts with hydrogen bonds while another portion of the molecule is essentially a hydrocarbon. Such molecules are usually actively excluded from the water phase and readily move into the cell membrane. Hence, most lipid molecules are absorbed by passive mechanisms. An important conclusion that derives these general features is that the rate of absorption of very hydrophylilic compounds is usually determined by the rate of carrier mediated transport by the membrane. In contrast, the rate of absorption of hydrophobic compounds is usually <u>not</u> dictated by events in the membrane but, rather, by the rate of events occurring in the bulk water phase.




During digestion a number of enzymes and surface active agents are secreted into the gastrointestinal tract. Acid lipase is secreted by glands located at the base of the tongue. Additional lipases, colipase, endo- and exopeptidases and amalyses are secreted by the pancreas. High concentrations of surface active bile acids also are secreted into the GI tract during a meal. As illustrated by Fig. 5, maintenance of high concentrations of bile acid in the proximal intestine depends upon an intact enterohepatic circulation. The total pool of bile acids in the body equals approximately 2 g. This pool is reabsorbed, primarily in the ileum, and is cycled through the liver approximately 6 times each day, so that the actual rate of bile acid secretion is approximately 12 g/day. Normally about 0.5 g of bile acid is synthesized by the liver each day and approximately 0.5 g is lost into the feces. If the ileal reabsorptive sites are destroyed, it is impossible for the liver to maintain adequate bile acid concentrations proximally. Even if hepatic bile acid synthesis increased 3 fold, to 1.5 g/day, this amount would be well below the concentrations necessary to maintain a secretory rate of 12 g/day.

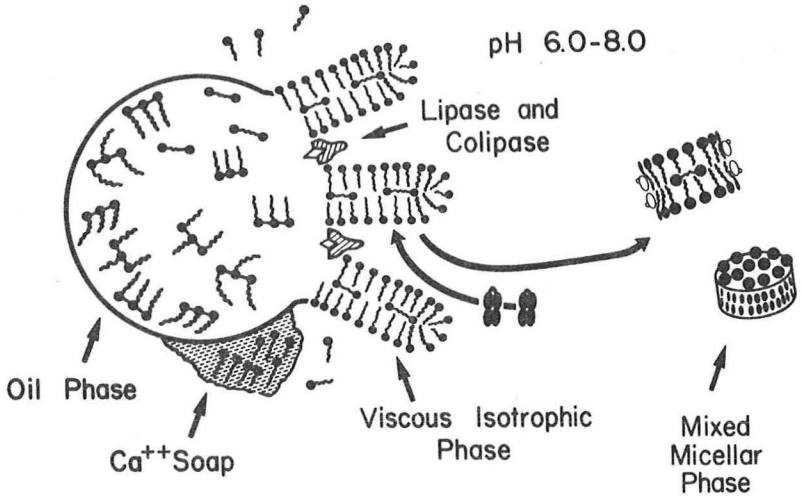
## IN THE STOMACH

pH 2.0-4.0



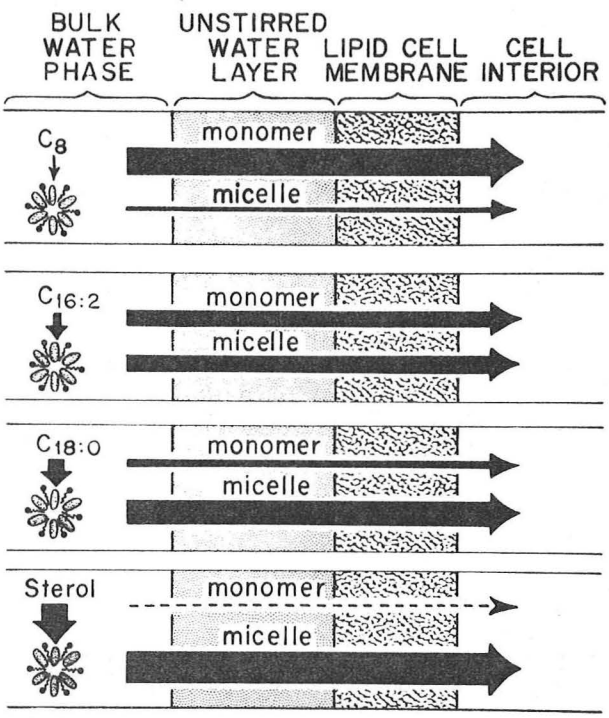

A) Fat and Fat Soluble Vitamins. Typical western diets contain 80-120 g of fat each day. The vast majority of this fat is in the form of triglycerides, i.e., 3 long chain fatty acids esterified to the alcohol glycerol. Initial digestion of triglyceride may take place under the action of lingual lipase. This enzyme is an acid lipase which actively hydrolyzes triglyceride molecules to free fatty acids and monoglycerides at the acid pH's that exist within the stomach. However, at these acid pH values, the fatty acids do not become ionized, and hence remain largely associated with the triglyceride phase of the diet. Such "predigestion" however, may be quantitatively important, particularly in young infants where the digestion of fat droplets in milk may take place to a significant degree under the influence of this lingual lipase (Fig. 6).

## IN THE JEJUNUM

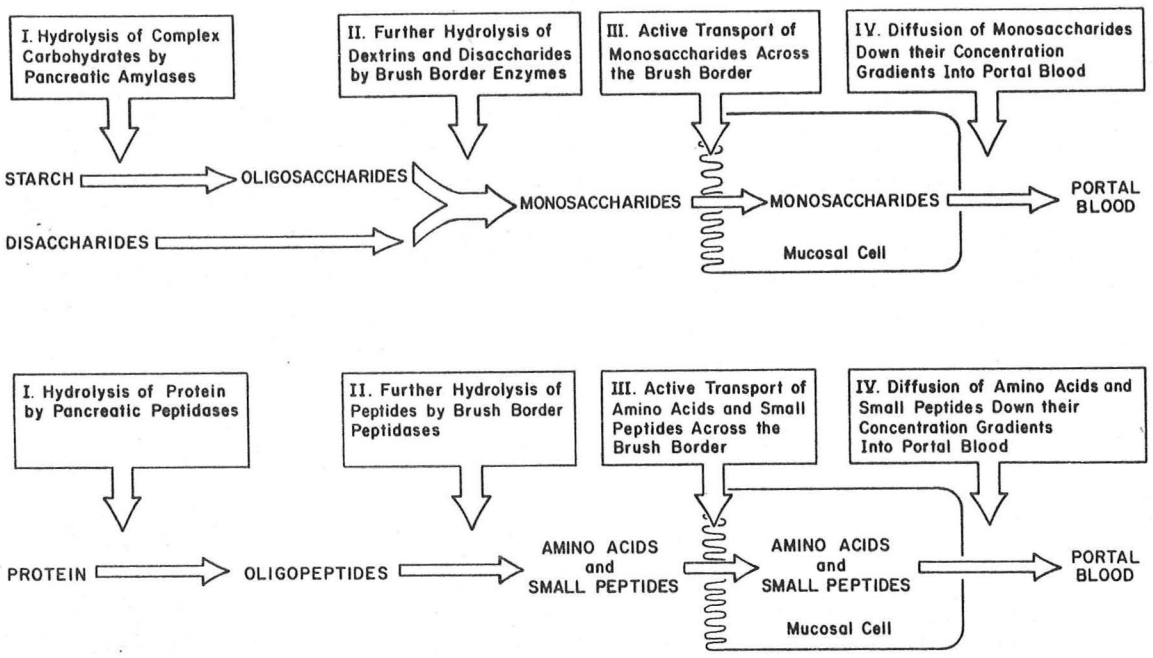



In the jejunum the remaining undigested triglyceride is mixed with lipase and colipase enzymes derived from the pancreas and with the bile acid derived from the liver. The colipase molecule maintains the attachment of the lipase molecule on the fat droplet in the presence of the bile acids. The triglyceride molecules are digested faster by the lipase than the products (fatty acids and monoglycerides) can be removed from the triglyceride particle and absorbed. Hence, these products tend to accumulate on the outside of the fat droplet as liquid crystals. In the presence of adequate concentrations of bile acid, however, these liquid crystals are progressively removed and form mixed micelles with the bile acids (Fig. 7). In addition, in the presence of calcium ion, some fatty acid may form insoluble calcium soaps. The magnitude of calcium soap formation is apparently dictated by the relative concentrations of monoglycerides and free fatty acids at the site of interaction: in general, the presence of monoglycerides inhibits calcium soap formation. Thus, during the process of digestion, four separate phases can be identified in small bowel aspirates. These include an oil phase of triglyceride, a viscous isotrophic phase of liquid crystals, mixed micelles and calcium soaps.

The mixed micelles containing the products of lipid digestion (including, probably, the fat soluble vitamins) diffuse up to the region of the intestinal brush border membrane. Here, the free fatty acids, monoglycerides and other components of the mixed micelle diffuse passively through the intestinal membrane and are absorbed into the enterocyte. This absorbed process probably takes place primarily through a monomer phase in equilibrium with the mixed micelles although it is still possible that there is some type of interaction between the micelle and microvillus membrane. Once within the cytosolic compartment of the enterocyte, the lipids are esterified and reformed into a lipid droplet. This lipid droplet is then coated with surface active agents such as free cholesterol and phospholipid and specific apoproteins (particularly apoB) are synthesized within the enterocyte and also added to the lipid interface. This nascent chylomicron particle is then extruded from the base of the intestinal epithelial cell, enters the intestinal lymphatic vessel and, ultimately, reaches peripheral circulation.




It should be noted that the dependency of the rate of absorption of a particular lipid on the presence of bile acid cells is largely determined by the hydrophilicity of that molecule. As illustrated in Fig. 8, for example, during the digestion of medium chain length triglyceride molecules most of the individual fatty acids partition into the monomer phase in equilibrium with the bile acid micelles. This occurs because of the greater hydrophilicity of these molecules. During the digestion of lipids which are less hydrophilic (more hydrophobic) a greater proportion of the reaction products become associated with the micellar phase. Hence, the less hydrophilic a molecule the more dependent it is upon the presence of adequate concentrations of bile acids in the intestinal lumen. Thus, the diseases which interfere with the enterohepatic circulation of bile acids may result in only a mild defect in triglyceride digestion and absorption but may interfere totally with the absorption of very nonpolar molecules such as cholesterol and the fat soluble vitamins.




B) Proteins and Carbohydrate. The major steps involved in the digestion and absorption of dietary carbohydrate and protein are outlined in Fig. 9, and may be compared with the major steps involved in the digestion and absorption of dietary fat shown in Fig. 7. As in the case of lipid digestion, the physiologically important breakdown of complex carbohydrates and proteins occurs in the proximal small bowel, where pancreatic amylase digests dietary starches to oligosaccharides and pancreatic peptidases split protein into oligopeptides (Step I). These products are polar and diffuse up to the luminal border of the epithelial cell, without the intervention of the bile acid micelle, where further digestion of the short-chain-length carbohydrates and peptides takes place under the influence of enzymes located on the outer surface of the microvillus membrane (Step II). The very polar, and therefore water-soluble monosaccharides, amino acids, and short-chain peptides released by these enzymes are then taken up into the epithelial cell by specific, carrier-mediated, energy-linked transport systems. After reaching the cytosolic compartment, these molecules then diffuse out the base of the epithelial cell and enter the blood capillary of the intestinal villus. Thus the products of the digestion of dietary carbohydrates and proteins are carried in the portal vein directly to the liver.

There are several fundamental differences between the digestion and absorption of these dietary components and the process described earlier for the uptake of dietary lipids. The uptake of lipids uniquely requires the presence of bile acids within the intestinal lumen, the assembly of chylomicrons within the cytosolic compartment of the epithelial cell, and an intact intestinal lymphatic system: These are not required for the digestion and absorption of dietary protein and complex carbohydrates. It is to be anticipated, therefore, that diseases that disturb the functional integrity of the pancreas and of the epithelial cell lining of the small bowel would cause severe maldigestion or malabsorption of all three major components of the diet, whereas diseases that disturb the normal enterohepatic circulation of bile acids, the assembly of the chylomicron, or the integrity of the intestinal lymphatics would result in a selective maldigestion or malabsorption of dietary fat, i.e., isolated steatorrhea.

## Section 4: TEST FOR MEASURING ABSORPTION IN MAN

Many tests have been described for use in the differential diagnosis of malabsorption syndromes. A number of these, however, are of little value despite their continued use in many hospitals. In this section we will discuss only five procedures: qualitative stool fat determination, quantitative stool fat determination, quantitative stool nitrogen determination, xylose absorption test, vitamin $B_{12}$ absorption test, and the small bowel biopsy. The specific information obtained from each of these examinations as well as the possible sources of error in their performance will be outlined. In the great majority of cases, the physician who has a sound understanding of the normal mechanisms of intestinal absorption will be able to arrive at the proper diagnosis using these relatively few, commonly available diagnostic tests.

a) Quantitative stool fat determination. A quantitative chemical determination of fecal fat is the most reliable measure of steatorrhea. In the normal individual the amount of fat appearing in the stool is relatively constant despite changes in the quantity of dietary fat. When fat intake is near zero the fecal fat output equals approximately 2.9 g per day. Presumably, this is the amount of fat that is derived from endogenous sources such as sloughing of mucosal cells and bacterial lipids. The fecal content of fat increases to 4.1 ± 0.5 g per 24 hr and 8.7 ± 0.7 g per 24 hr in subjects receiving 100 g and 200 g, respectively, of fat in their daily dietary intake. Thus, in the individual with normal gastrointestinal function fecal fat is usually <7% of the dietary fat intake; in the face of the typical daily fat intake of 60 to 100 g this is approximately equivalent to an excretory rate of <6 g per 24 hr. In the patient with compromised digestive or absorptive capacity, however, the amount of fat excreted in the stool is more directly related to the amount of fat intake in the diet.

A number of conditions should be met in order to obtain a meaningful quantitative determination of fecal fat output. The patient must be eating a significant amount of fat (60 to 100 g per day) for several days before as well as during the 72-hr stool collection. Poor food intake during the collection period may lead to erroneously low or even normal values for fecal fat excretion in patients with mild steatorrhea. Regular bowel movements must be insured and the stool collection must be complete. Artifactually high

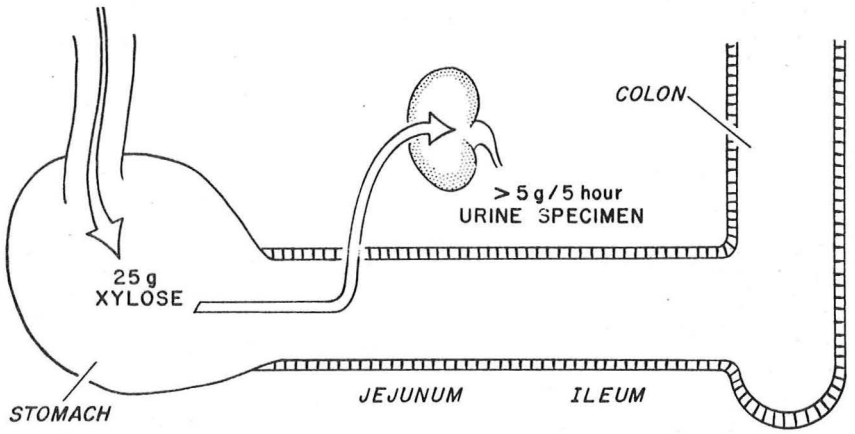
values may occur in patients ingesting large quantities of castor oil or nut oils.

The Van de Kamer method is the most commonly utilized procedure for the chemical determination of fecal fat content. Recently it has been pointed out that this method may lead to incomplete extraction and quantitation of medium chain-length fatty acids; hence, this method may underestimate the quantity of fecal fats in patients whose diet has been supplemented with medium chain triglyceride oils. This artifact, however, apparently can be obviated by modification of the basic Van de Kamer procedure.

b) Fecal nigrogen. Determination of fecal nitrogen provides an indirect measure of protein absorption. The patient should be on a balanced protein diet and stool should be collected for at least 72 hr. Depending upon the laboratory, the normal fecal nitrogen excretion equals 2.0 to 2.5 g per 24 hr while on a 80- to 100-g protein intake. Desquamation of epithelial cells, secretion of digestive fluids containing protein, and leakage of plasma proteins across the intestinal mucosa contribute to the intraluminal nitrogen pool. Excessive leakage of plasma proteins into the intestinal lumen may artifactually elevate fecal nitrogen levels. Provided significant protein-losing enteropathy is not present, however, quantitative fecal nitrogen excretion data provide a useful measure of protein malabsorption.

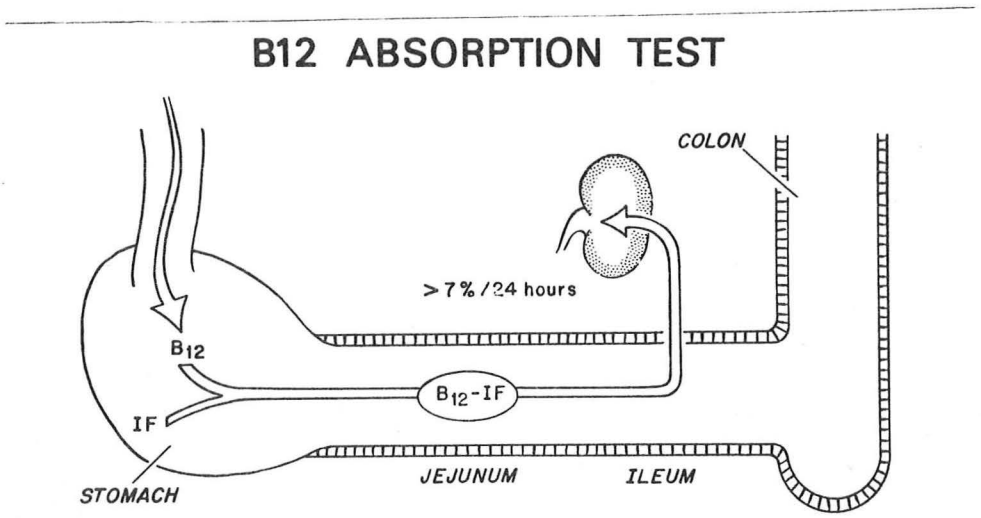
c) Xylose absorption test. The xylose absorption test commonly is regarded erroneously as a measure of carbohydrate absorption. Xylose, a five-carbon monosaccharide, is absorbed primarily by passive means in the proximal small intestine. The mechanism of absorption probably is quite different from the carried-mediated transport involved in the absorption of six-carbon monosaccharides of dietary importance. The xylose absorption test, nevertheless, is extremely valuable as a means of evaluating certain specific intestinal functions in malabsorption syndromes.

## XYLOSE ABSORPTION TEST




The test usually is performed by the oral administration of 25 g of xylose to a fasting patient (Fig. 10). After the patient empties his bladder, a 5-hr urinary collection is obtained during adequate fluid intake to maintain satisfactory urine flow. There are a number of possible artifacts that may enter into this test that must be avoided. Vomiting or delayed gastric emptying will lead to artifactually low urinary values. Similarly, inadequate hydration or decreased effective circulating volume, intrinsic renal disease, and the presence of massive ascites will lead to decreased urinary clearance of xylose and, again, an artifactually low urinary excretory value. In most series <4.5 g of xylose is excreted in normal subjects in the first 5-hr urinary collection; however, it should be recognized that the mean normal excretory values decrease with age, particularly in patients over 50 years of age.

Provided that the test has been properly done and none of the artifacts outlined above is present, then a very low value for xylose excretion, usually <2.5 g per 5 hr, may be seen in two clinical situations: (1) in the presence of massive bacterial overgrowth in the proximal small intestine where there is uptake and metabolism of xylose by the organisms, and (2) in disease states where there is significant loss of the functional integrity of the jejunum. Administration of appropriate antibiotics will correct the xylose absorption test in the former but not in the latter situation.




d) $B_{12}$ absorption test. The absorption of vitamin $B_{12}$ involves the binding of the vitamin with intrinsic factor in the stomach, transport of the $B_{12}$-intrinsic factor complex through the proximal small intestine, binding of the complex to specific sites in the ileum, and, finally, absorption of $B_{12}$ into the protal circulation. In the conventional Schilling test a flushing dose of parenteral vitamin $B_{12}$ also is administered so that a significant amount of the oral dose of radiolabeled $B_{12}$ is excreted in the urine. Depending upon the particular laboratory, excretion of >5 to 8% per 24 hr of the administered radiolabeled $B_{12}$ usually is regarded as normal (Fig. 11).

There also are a number of possible sources of error in the performance of the Schilling test. Vomiting after the administration of the radiolabeled vitamin will lead to artifactually low urinary values. Low excretory values are seen in patients who have had a gastrectomy apparently because the test dose of radiolabeled $B_{12}$ passes too quickly through the stomach to allow adequate binding to intrinsic factor. Finally, decreased extracellular volume or intrinsic renal disease also may result in decreased urinary excretion. In contrast to these errors, contamination of urine with feces containing unabsorbed radiolabeled $B_{12}$ will result in falsely elevated values.

Provided that none of these artifact is present and provided that the patient has adequate intrinsic factor, then very low excretory rates, usually <1 to 3% per 24 hr, are seen in two situations: (1) in the presence of massive bacterial overgrowth or infestation with certain tapeworms in the proximal small intestine where there is binding of the $B_{12}$-intrinsic factor complex, and (2) in disease states that lead to significant loss of functional integrity of the ileum. Administration of appropriate antibiotics will correct the Schilling test in the former but not in the latter situation.

e) Peroral small intestinal biopsy. Suction and hydraulic biopsy instruments for procurement of intestinal mucosa have considerably facilitated diagnosis of malabsorption disorders, yet errors of interpretation may occur. Knowledge of the normal histology at various levels of the gastrointestinal tract is necessary in order to make valid comparisons with diseased tissues, and an awareness of special preparations and staining techniques to demonstrate histological findings peculiar to certain diseases will greatly facilitate diagnosis. As outlined in Table I, the histological findings in at least five specific disorders affecting the small bowel are unique enough to be essentially diagnostic; these include gluten enteropathy, Whipple's disease, a-β-lipoproteinemia, amyloidosis, and mast cell disease. An additional nine conditions are listed where the histological changes are compatible with, but not necessarily diagnostic of, specific diseases. Thus, properly processed and interpreted, the small intestinal biopsy is invaluable in diagnosing those diseases that cause malabsorption by involving the proximal small intestinal mucosa.

## SYMPTOMS OF MALABSORPTION

1) Weight Loss
2) Diarrhea, Change In Stool Character
3) Evidence Of Protein Malnutrition
4) Hypoprothrombinemia
5) Evidence Of Vitamin A Deficiency
6) Evidence Of Water Soluble Vitamin Deficiency
7) Anemia
8) Metabolic Bone Disease
9) GI Bleeding
10) Severe Secretory Diarrhea

Section 5: GENERAL SYMPTOMS AND SYNDROMES OF MALABSORPTION

As illustrated by the data in Fig. 12, the symptoms associated with malabsorption syndromes are relatively nonspecific. Weight loss can result if the total loss of calories exceeds the metabolic needs of the patient. However, many patients will increase food intake to a point at which weight loss is minimal. Perhaps the most common symptom of malabsorption is a change in the character in the stool and, in some cases frank diarrhea. However,

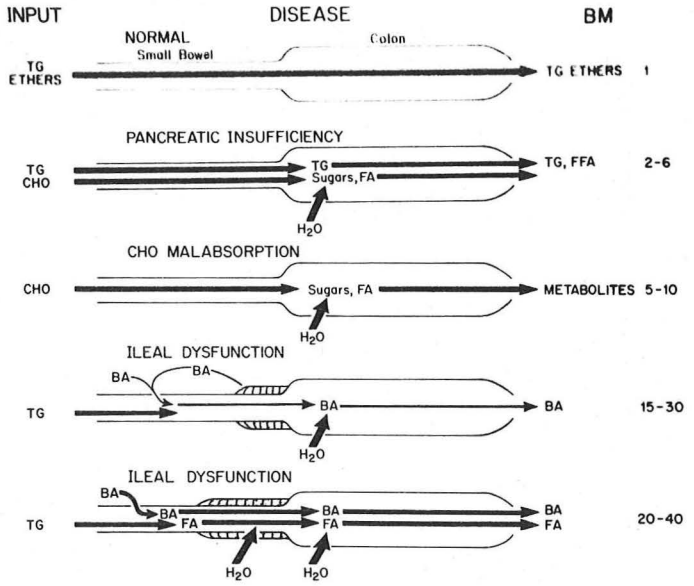
Table I. Summary of the principal histological findings in small bowel biopsies that either are diagnostic of or are compatible with specific intestinal diseases causing malabsorption

1. Biopsies that are essentially diagnostic of

A. Gluten enteropathy: villous atrophy with alteration of the surface epithelium, hypertrophy of the crypt epithelium, and infiltration of the lamina propria with chronic inflammatory cells.
B. Whipple's disease: infiltration of lamina propria with macrophages containing periodic acid-Schiff positive cytoplasmic inclusions, loss of villous structure, and flattening of the mucosal surface to varying degrees; osmium-fixed sections stained with Toluidine blue reveal characteristic bacilli-like structures beneath the basement membrane and between macrophages.
C. A-β-lipoproteinemia: normal villous structure but biopsies taken in fasting state show numerous cytoplasmic droplest that stain with fat stains.
D. Amyloidois: presence of amyloid deposits seen after staining with Congo red; Congo red-positive areas show birefringence with polarizing light.
E. Mast cell disease: large number of mast cells in lamina propria, muscularis mucosa, and submucosal areas.

2. Biopsies that are compatible with

F. Radiation enteritis: acute changes consist of decreased mitoses in the crypt cells, shortening of the villi and crypts and infiltration of the lamina propria with plasma cells and polymorphonuclear leukocytes; chronic changes involve connective tissue proliferation with thickening and loss of vascularity in the submucosa.
G. Lymphangiectasia: dilation of lacteals and lymphatics in the lamina propria and submucosa causing distortion of some villi but villous and crypt epithelium are essentially normal; lymphatics may contain lipid-filled macrophates.
H. Tropical sprue: varying degrees of villous atrophy with pleomorphic plasma cells in the lamina propria; infiltration and destruction of crypts by pleomorphic lymphoid cells; dilation of mucosal lymphatics.
I. Nongranulomatous jejunitis: flattening and loss of villi with distortion of crypts and mononuclear infiltration of lamina propria; no granulomas seen.
J. Scleroderma: collagenous encapsulation of Brunner's gland with fibrosis and inflammatory cell infiltration in the submucosa.
M. Hypogammaglobulinemia: absence or flattening of villi and absence or paucity of plasma cells in the lamina propria; infiltration of the submcosal tissues with lymphocytes.
N. Parasites: varying degrees of blunting and shortening of the villi with cellular infiltration of the lamina propria; may see Strongyloides larva in the crypts, Schistosoma mansoni ova in the mucosa and submucosa, Capillaria worms penetrating the mucosa, or Giardia trophozoites in the intervillous spaces.




this is extremely variable. As shown in Fig. 13 the number of bowel movements in bowel absorption can vary anywhere from essentially one to multiple. Depending upon the underlying defect patients will have an element of osmotic and secretory diarrhea associated with the malabsorption. For example, in situations in which there is maldigestion or malabsorption of carbohydrates in the small intestine, there is generation of osmotically active materials in the colon as the carbohydrates are metabolized by bacteria. Similarly, in those situations in which there is an element of bile acid malabsorption, there can be stimulation of colonic secretions due to the added amounts of bile acid that reach the colon. Thus, on the one hand, one may have patients with pancreatic insufficiency who have very large amounts of steatorrhea but who have only 2 to 4 semiformed bowel movements per day. At the other extreme are patients with significant ileal dysfunction who may have low to modest degrees of steatorrhea but who have very significant volume output of a secretory diarrhea results in 20-40 bowel movements per day. Thus, while a change in stool character is common in the malabsorption syndromes there is no characteristic pattern that would allow one to separate this group of diseases from patients, for example, who have primary secretory or osmotic diarrheas. It would be essential, therefore, in the differential diagnosis to identify that there is excessive fat in the stool, i.e., steatorrhea.

The remaining findings in malabsorption syndromes are far less common. Under circumstances where there is maldigestion or absorption of protein, evidence of protein malnutrition may be present in peripheral tissues with, for example, changes in hair, skin and nails. Evidence of isolated fat soluble vitamin deficiencies may develop and make themselves manifest as a severe bleeding problem or a change in night vision. Similarly, a variety of anemias may be an early manifestation of malabsorption. Typically diseases associated with extensive destruction of the jejunum can result in folate deficiency states whereas diseases effecting ileal function are associated with vitamin $B_{12}$ deficiency states. Metabolic bone disease can be a subtle and fairly common manifestation of underlying malabsorption and can be due to a complex defect in both vitamin D absorption and in the complexing of calcium in the gut lumen with unabsorbed fatty acids. Finally, GI bleeding is a very uncommon finding in the malabsorption syndromes and, in general, should suggest that a chronic diarrhea is due to some other lesion such as a tumor or an inflammatory bowel syndrome. However, some specific causes of malabsorption, such as Whipple's disease, are associated with occult blood in the stool.

Thus, the symptoms of malabsorption syndrome are relatively nonspecific but the disease is most commonly made manifest by a change in the character of the stool and associated weight loss. Ultimately, the diagnosis must be recognized by direct demonstration that there is excessive fat in the stool and hence either maldigestion or malabsorption of lipids.

## Section 6: SPECIFIC MALABSORPTION SYNDROME

The values for the major absorptive studies in diseases that result in malabsorption are presented in Table II. These laboratory data were derived from over 1000 cases reported in the literature. In order to be included in this series an acceptable evaluation of stool fat (expressed in grams per 24 hr or percentage of intake) was required. Insofar as possible the diseases have been grouped according to the site of the defect in digestion or absorption. Some disorders produce more than a single defect, while in others the site of the defect remains poorly understood.

### 1. Insufficient Intraluminal Pancreatic Enzyme Activity

As shown in Fig. 7, the first major step in fat absorption is that of hydrolysis of triglyceride to fatty acid and β-monoglycerides. Diseases that result in a marked decrease in secretion of pancreatic enzymes cause malabsorption because of diminished enzymatic activity in the proximal small intestine. In this category of illnesses one would anticipate that maldigestion and malabsorption would involve fat, protein, and carbohydrate but that the tests of intestinal mucosal integrity, i.e., xylose and $B_{12}$ absorption and mucosal biopsy, would be normal.

The specific diseases that fall into this category are shown in group 1, Table II, and include chronic pancreatitis, pancreatic carcinoma, pancreatic resection, and cystic fibrosis. The common defect in all of these conditions is reduction of enzymatic activity either because of destruction of the gland or because of ductal obstruction. In general the steatorrhea is severe and in this series varied from 25 to 44 g per 24 hr (from 30 to 45% of intake). As anticipated, there also was significant azotorrhea with fecal nitrogen excretions ranging from 4.2 to 7.5 g per 24 hr. Insofar as they have been reported xylose absorption and small intestinal biopsies usually are normal. $B_{12}$ absorption studies also are normal in the majority of cases although recent reports have indicated that values may be reduced into the range of 2 to 7% per 24 hr in approximately 40% of cases, and a possible role for pancreatic enzymes in absorption of vitamin $B_{12}$ has been raised. It should be emphasized, however, that very low absorption rates, <1 to 2% per 24 hr are virtually never seen in malabsorption due to pancreatic insufficiency. Thus, diseases that result in pancreatic insufficiency commonly produce severe steatorrhea and azotorrhea while small bowel function as evidenced by the xylose and $B_{12}$ absorption studies and the small bowel biopsy is usually normal.

### 2. Insufficient Intraluminal Bile Acid Activity

In this section clinical conditions are discussed in which insufficient intraluminal bile acid activity presumably is the predominant, if not the sole cause of the development of malabsorption. This group of illnesses includes those disease states where there is diminished secretion of bile acids into the intestine or where there is intraluminal bacterial alteration of the bile acids.

Biliary Obstruction and Liver Disease. In the presence of biliary obstruction and liver disease at least three steps in normal bile acid metabolism may be altered; these include (1) uptake by the liver, (2) de novo synthesis by the liver, and (3) secretion into the bile. A defect in hepatic intake is suggested by the delayed clearance of intravenously administered labeled bile acids from the circulation observed in both acute and chronic liver disease. In this circumstance significant urinary losses of bile acid may occur. Diminished bile acid synthesis also may contribute to the low bile acid levels seen in patients with predominantly hepatocellular damage. In some instances patients demonstrate a relationship between the severity of steatorrhea and the severity of liver dysfunction. This possibility is

TABLE II. Representative values in specific diseases of the major diagnostic tests used to differentiate various malabsorption syndromes

| Disorder | A. Fecal fat excretion | B. Fecal nitrogen excretion | C. Urinary xylose excretion | D. Urinary vitamin $B_{12}$ excretion |
|---|---|---|---|---|
| | g/24 hr | g/24 hr | g/5 hr | %/24 hr |
| Representative normal values | <6 | <2.0 | >4.5 | >7.0 |
| 1. Insufficient intraluminal pancreatic enzyme activity | | | | |
| A. Chronic pancreatitis | 37 ± 4.5 | 4.7 ± 0.6 | 6.1 ± 0.7 | |
| B. Pancreatic carcinoma | 41 ± 7.0 | 6.0 ± 0.9 | 5.5 ± 0.6 | 8.4 ± 2.0 |
| C. Pancreatic resection | 44 ± 4.3 | 7.5 ± 1.0 | | |
| D. Cystic fibrosis | 25 ± 4.1 | 4.2 ± 0.6 | | |
| 2. Insufficient intraluminal bile acid activity | | | | |
| E. Extrahepatic biliary obstruction | | 1.2 ± 0.2 | | |
| F. Intrahepatic disease with jaundice | 16 ± 2.0 | 1.2 ± 0.1 | 4.3 ± 0.9 | 11.0 ± 1.0 |
| G. Intrahepatic disease without jaundice | 19 ± 3.0 | 1.6 ± 0.3 | 5.9 | |
| H. Cholecystocolonic fistula | 13 | 1.2 | | |
| I. Intestinal stasis syndrome | 17 ± 1.9 | 1.8 ± 0.2 | 3.0 ± 0.5 | 0.9 ± 0.3 |
| 3. Intramural small bowel disease | | | | |
| J. Gluten enteropathy | 28 ± 1.8 | 5.0 ± 1.2 | 2.0 ± 0.3 | 2.4 ± 1.0 |
| K. Tropical sprue | 16 ± 0.6 | | 2.2 ± 0.6 | 5.1 ± 1.3 |
| L. Skin disease | | | | |
| 1. Dermatitis herpetiformis | 9 ± 0.6 | | 3.0 ± 0.6 | 14.9 ± 1.3 |
| 2. Others | 8 ± 0.5 | | 4.0 ± 0.6 | 6.2 |
| M. Nongranulomatous jejunitis | 27 ± 5.4 | 0.6 | 3.4 ± 1.1 | 1.9 |
| N. Whipple's disease | 34 ± 4.8 | 3.8 ± 0.5 | 3.7 ± 0.4 | 12.8 ± 3.7 |
| O. Amyloidosis | | | | |
| 1. Primary | 22 ± 3.2 | 4.9 ± 0.7 | | 6.0 ± 1.0 |

| | | | | |
|---|---|---|---|---|
| 2. Secondary and multiple myeloma | 15 ± 2.9 | 3.0 ± 0.1 | 2.1 ± 0.3 | |
| P. Eosinophilic gastroenter- | 14 ± 2.1 | | 2.3 ± 0.7 | 3.0 |
| Q. Food allergy | 19 ± 6.1 | 0.7 | 11.2 | |
| R. Small bowel ischemia | | | | |
| 1. Atherosclerosis | 15 ± 1.6 | | 2.0 ± 0.5 | 6.8 |
| 2. Polycythemia vera | 20 | | | |
| 3. Vasculitis | 14 | | | |
| 4. Kohlmeier-Degos syndrome | 26 | | 1.9 | |
| S. Small bowel resection | | | | |
| 1. Jejunectomy | 9 | | | |
| 2. Massive resection or bypass | 49 ± 7.2 | | 2.3 ± 1.2 | 1.1 ± 0.5 |
| T. Intestinal lymphangiectasia | 23 ± 4.0 | 3.2 ± 1.0 | 7.8 ± 0.5 | |
| U. A-β-lipoproteinemia | 15 | | 6.2 ± 1.3 | 19.0 ± 2.6 |
| V. Lymphoma | 25 ± 2.8 | 2.4 | 2.2 ± 0.5 | 4.0 ± 0.8 |
| 4. Malabsorption caused by multiple defects | | | | |
| W. Zollinger-Ellison syndrome | 24 ± 2.4 | 3.0 ± 0.8 | 31 | |
| X. Scleroderma | 19 ± 2.0 | 2.1 ± 0.2 | 2.6 ± 0.4 | 11.5 ± 2.0 |
| Y. Ileal dysfunction | | | | |
| 1. Ileal resection | 24 ± 2.8 | 2.9 ± 0.4 | 4.8 ± 1.9 | 3.3 ± 0.4 |
| 2. Ileal Crohn's disease | 15 ± 2.3 | 4.0 ± 1.1 | 5.7 ± 0.7 | |
| Z. Postgastrectomy | 16 ±15.0 | 6.5 ± 2.3 | 3.1 ± 0.6 | 2.7 ± 1.5 |
| AA. Radiation enteritis | 32 ±15.0 | 6.5 ± 2.3 | 3.1 ± 0.6 | 2.7 ± 1.5 |

supported by isotope studies that have demonstrated a low pool size and daily production rate of bile acid in some hepatitis patients.

Regardless of the mechanism, any one of these defects may lead to diminished concentrations of bile acid in the intestinal contents, inadequate micellar solubilization of lipids, and subsequent steatorrhea. Although intraluminal bile acid concentrations have been measured in only a few of these patients, in these cases steatorrhea has been shown to be associated with low intraluminal concentrations of conjugated bile acids and impaired lipid micellar solubilization.

The steatorrhea of uncomplicated biliary obstruction and liver disease is usually mild and, on the average, varies from 15.5 to 18.1 gm/24 hr. Since bile acid is required only for the absorption of lipids, the other tests of absorption, eg, fecal nitrogen, xylose absorption, and vitamin $B_{12}$ absorption are normal. Serum albumin may be depressed and serum globulin elevated as would be appropriate for the underlying liver disease.

Cholecystocolonic Fistual. The cholecystocolonic fistula is the second most common fistula between the gallbladder and the gastrointestinal tract. The presence of a stone in the common bile duct with the development of a fistulous communication between the gallbladder and the colon leads to shunting of conjugated bile acids away from the small intestine. This diagnosis is suggested by the presence of contrast medium only in the proximal colon following intravenous cholangiography. The entry of increased quantities of bile acids into the large bowel presumably is responsible for the diarrhea occurring in these patients since perfusion studies have shown that bile salts stimulate the secretion of water and electrolytes in the colon.

The association between cholecystocolonic fistulae and steatorrhea has been described only rarely. The shunting of bile acids from the proximal small bowel results in diminished micellar solubilization and subsequent intestinal malabsorption of lipid. Correction of fat malabsorption follows the administration of bile acids orally.

The data again demonstrate that the level of steatorrhea is mild in patients with diminished intraluminal bile acids secondary to cholecystocolonic fistula (12.2 ± 1.9 gm/24 hr). Insofar as they have been performed, other tests of absorption are usually normal.

Intestinal Stasis Syndrome. A number of anatomical and motility derangements of the gastrointestinal tract, eg, multiple strictures, surgical blind loops, afferent loop dysfunction, enteric strictures and fistulae, multiple jejunal diverticula, diabetic neuropathy, and scleroderma, may give rise to the intestinal stasis or blind loop syndrome. The characteristic feature of this syndrome is the presence of massive bacterial overgrowth in the proximal small bowel secondary to stasis of intestinal contents.

Under normal fasting conditions, bacterial counts of fluid from the proximal small bowel rarely exceed $10^2$ to $10^3$ organisms per milliliter, and most of the bacteria are aerobes or facultative anaerobes. In contrast, bacterial counts in intestinal fluid of patients with the intestinal stasis syndrome may reach $10^8$ or $10^9$ organisms per milliter. Anaerobic bacteriologic studies have demonstrated that bacteroides may be the most prominent organisms

encountered in this syndrome, but coliform, bactobacilli, enterococci, and diphtheroids also may be present. Several of these species are able to deconjugate bile acids. Analysis of the intestinal contents of patients with intestinal stasis usually reveals a decrease in the concentration of conjugated and an increase in the concentration of unconjugated bile acids. The total concentration of bile acids may be normal or low. While it is currently unclear whether malabsorption in this disease results from a direct toxic effect of unconjugated bile acids on the intestinal mucosa or from the decrease in concentration of conjugated bile acids, most evidence favors the latter possibility. It has been demonstrated, for example, that while unconjugated bile acids impair intestinal absorption and fatty acid esterification in vitro they do not exert such effects in vivo. It also has been shown that while unconjugated bile acids produce morphologic alterations in the intestinal mucosa in vitro, most patients with the intestinal stasis syndrome have essentially normal mucosal architecture in the proximal mucosal architecture in the proximal small bowel. Finally, the absorptive defect has been corrected by the administration of conjugated bile acids despite the continued presence of significant concentrations of unconjugated bile acids in the intestinal contents.

The enterohepatic circulation of increased quantities of unconjugated bile acids apparently increases the load on the hepatic conjugating mechanism. As a result, the availability of taurine becomes relatively rate limiting and, consequently, a higher percentage of the bile acids than normal becomes conjugated with glycine.

In addition to the effect of bacterial overgrowth on bile acid metabolism, these organisms also have the capacity to bind the vitamin $B_{12}$-intrinsic factor complex and so compete with the specific binding sites in the ileal mucosa. Hence, a very low vitamin $B_{12}$ absorption test with or without intrinsic factor is characteristic of the intestinal stasis syndrome. Less commonly, the xylose absorption test also may be abnormal. This abnormality has been attributed to bacterial utilization of this five-carbon sugar or to inhibition of sugar transport by unconjugated bile acids.

The characteristic laboratory findings in the intestinal stasis syndrome are also presented in Table II. As is true of the other types of steatorrhea resulting from an absolute or relative deficiency of bile acid in the proximal small intestine, the degree of steatorrhea typically is mild, averaging 17.5 ± 10.5 gm/24 hr. Fecal nitrogen excretion rarely is elevated and in most reported cases is normal. Vitamin $B_{12}$ absorption invariably is very low (0.9%/24 hr ± 0.8%) while xylose absorption may be low or normal. These patients, as noted above, also excrete an excessive amount of $^{14}CO_2$ after administration of glycine-1-$^{14}$C-cholic acid. The characteristic, essentially pathonomonic, feature of the intestinal stasis syndrome is that these various abnormalities in absorptive tests return essentially to normal following the administration of appropriate antibiotics (usually tetracycline) for three days.

Ileal Dysfunction Syndrome. As outlined in the first section of this protocol, the second or micellar solubilization phase of fat absorption depends upon the presence of adequate concentrations of bile salts in the jejunal contents. The capacity of the body to maintain this concentration, in turn, depends upon the ability of the small intestine to reabsorb bile salts. If ileal bypass, resection, or disease (ie, granulomatous or radiation

ileitis) is present, bile salt absorption is compromised, and unabsorbed bile salts enter the colon and are lost in the feces. In such conditions kinetic studies have demonstrated a grossly shortened halflife and diminished pool of bile acid suggesting virtual loss of the enterohepatic circulation. Other studies, however, suggest that significant reabsorption of bile salts does occur with ileal dysfunction. Studies in monkeys, for example, indicate that resection of the distal one third of the small bowel is equivalent to a 50% interruption of the enterohepatic circulation. It now appears therefore that the ability to maintain normal bile acid levels in the jejunum largely depends upon the extent of ileal involvement. It has been estimated, for example, that patients with less than 100-cm resection of the ileum are able to compensate for bile salt loss. Under these circumstances a number of events have been observed: (1) Hepatic synthesis increases several fold. (2) The ratio of primary to secondary bile acids is increased in the feces. The increased concentrations of bile acids in the colon appear to influence the bacterial alterations of bile acids since 7-dehydroxylation is reduced and deoxycholic acid may be absent in bile and feces. (3) The relative amounts of bile acid conjugated with glycine and taurine is altered so that the glycine:taurine ratio of bile salts in duodenal fluid may be increased to as high as 15:1 (normal, 3:1). (4) Steatorrhea is mild, usually <20 gm; whereas, diarrhea is often a more important clinical finding than steatorrhea and presumably is due to inhibition of absorption or secretion of water and electrolytes by bile salts in the colon. In these patients cholestyramine, a bile acid sequestrant, may benefit the diarrhea without increasing steatorrhea significantly.

In patients with more extensive ileal involvement, the picture described above is somewhat altered. Although hepatic synthesis of bile salts increase at an enhanced rate, it is insufficient to maintain adequate levels of bile salts in the jejunum for effective micellar solubilization. Steatorrhea is more severe which reflects, in part, both an inadequate bile acid pool and decreased absorptive surface area. The bile acids of bile and feces contain a normal or high level of secondary bile salts indicating bacterial dehydroxylation is taking place. Diarrhea remains a problem but probably occurs by a different mechanism for it has been corrected by the replacement of dietary long-chain FAs with medium-chain FAs but not by cholestyramine. It is suggested that the cathartic effect of long-chain FAs is due to stimulation of water and electrolyte secretion by the ileum and colon.

As shown in Table II, the degree of steatorrhea varies, on the average, from 15 to 30 gm/24 hr and is determined undoubtedly by the amount of ileal function lost in particular patients. In general, the steatorrhea is more severe when the dysfunction is secondary to ileal resection than to Crohn's disease of the distal small bowel. However, it should be stressed that ileal resection does not produce as severe a defect in fat absorption as seen with massive intestinal resection or bypass, indicating that significant fat absorption still occurs in the proximal small bowel despite ileal dysfunction. Xylose absorption is usually normal unless there is concomitant jejunal involvement, while vitamin $B_{12}$ malabsorption is almost invariably present. This latter defect is not corrected by intrinsic factor or antibiotic therapy.

### 3. Intramural Small Bowel Disease

The third major step in fat absorption is uptake of the fatty acid and β-monoglyceride into the cell followed by esterification and chylomicron formation. In a number of diseases the primary pathology is found in the small intestine and presumably causes malabsorption by mechanisms that may vary from diffuse destruction of the mucosa to highly specific intracellular enzyme defects. In this category of diseases, the tests of intestinal function such as xylose and $B_{12}$ absorption and the small bowel biopsy are valuable in the differential diagnostic approach to the cause of malabsorption.

Gluten enteropathy. The characteristic histological abnormalities in gluten enteropathy are short, blunt villi, elongated crypts, abnormal epithelial cells at the luminal surface, and cellular infiltration of the lamina propria. In addition, under the electron microscope the microvilli of the surface epithelial cells are variably reduced in size and number and often appear fused at their bases. Many prominent lysosome-like structures and unattached ribosomes lie free in the cytoplasm of the epithelial cells. The basement membrane frequently is absent with numerous inflammatory cells interspersed among the epithelial cells. As a result of these marked structural changes throughout the jejunum and, in some cases, in the ileum there is poor absorption of a number of dietary constituents including fat, protein, and carbohydrate. Thus, characteristically (Table II) there is massive malabsorption of both fat (28 ± 1.8 g per 24 hr or 32% ± 4.4% of intake) and protein (5.0 ± 1.2 g per 24 hr). Since the disease most commonly produces extensive destruction of the jejunal mucosa, xylose absorption is uniformly low and in many cases is <2 g per 5 hr. Where the lesion extends into the ileum low $B_{12}$ absorption may be found while in other cases with less extensive involvement this test of ileal function is normal. As outlined in Table I, the histological findings in this disease are characteristic so that biopsy of the proximal small intestine usually is essentially diagnostic.

Tropical sprue, skin diseases, and nongranulomatous jejunitis. There are a number of other clinical entities in which the morphology of the villous absorptive cells is abnormal. They include tropical sprue, dermatitis herpetiformis, and other skin diseases and nongranulomatous peculiar to these entities are summarized in Table I. The common denominator in these diseases is a loss of villous structure and absorptive surface that presumably results in malabsorption of fat and other nutrients. In tropical sprue fecal fat averages 16 ± 0.6 g per 24 hr (13 ± 0.8% of intake) and the xylose absorption test is low (2.2 ± 0.6 g per 5 hr). Dermatitis herpetiformis and other skin lesions are associated with a very mild steatorrhea (8 to 9 g per 24 hr) and near normal xylose and $B_{12}$ absorption. In nongranulomatous jejunitis, a disease that some authors consider a variant of gluten enteropathy- there is more severe steatorrhea (27 ± 5.4 g per 24 hr) with values of 3.4 ± 1.1 g per 5 hr and 1.9% per 24 hr, respectively, for the xylose and $B_{12}$ absorption studies.

Whipple's disease. In contrast to gluten enteropathy, the morphological changes in Whipple's disease are most striking in the lamina propria. The normal cellular elements of the lamina are virtually replaced by macrophages containing periodic acid-Schiff positive glycoprotein within their cytoplasm (Table I). In addition, there are rod-shaped structures seen in the lamina propria that under the electron microscope have the typical features of

bacteria. The villous absorptive cells and mucosal surface area in Whipple's disease appear relatively well preserved yet in in vitro studies using tissue obtained by biopsy there is a decrease in capacity for amino acid transport and fatty acid esterification. Furthermore, there is morphological evidence to suggest that the delivery of triglyceride into the lymphatics also may be impaired.

These findings are reflected in the absorptive studies shown in Table ; patients with this disorder manifest severe malabsorption of both fat (34 ± 4.8 g per 24 hr or 50 ± 5.9% of intake) and protein (3.8 ± 0.5 g per 24 hr). In contrast to gluten enteropathy, however, the average value of xylose absorption (3.7 ± 0.4 g per 5 hr) is near normal as is $B_{12}$ absorption (12.8 ± 3.7% per 24 hr). As outlined in Table I, appropriately prepared sections of small intestinal biopsies are diagnostic of this disease.

Amyloidosis. Although the extent of amyloid involvement of various structures in the bowel wall is variable, the most frequent site is in the submucosal blood vessels. In familial Mediterranean fever and secondary amyloidosis deposition appears in the inner coats of the small blood vessels while parenchymal deposition occurs predominantly in the mucosa. On the other hand, in primary amyloidosis and amyloidosis associated with multiple myeloma, amyloid deposition is found in the outer coat of the small blood vessels while parenchymal deposition occurs predominantly in the muscularis externa. Mucosal architecture usually is normal until massive deposits destroy the glandular structures.

From the data presented in Table the absorptive defect is rather extensive in both primary and secondary amyloidosis. There is a moderate increase in both fecal fat (15 to 22 g per 24 hr) and fecal nitrogen (3.0 to 4.9 g per 24 hr) and marked depression of urinary xylose excretion (2.1 ± 0.3 g per 5 hr). The $B_{12}$ absorption test is near normal. Because diffuse involvement is common, biopsy of the small intestinal mucosa usually is diagnostic.

Eosinophilic gastroenteritis and food allergy. There is currently controversy as to whether these two clinical entities are distinct or whether they represent unrelated syndromes. Both, however, are associated with mild steatorrhea, as shown in Table II, but data on other aspects of absorption are limited.

Small bowel ischemia. The syndrome of intermittent arterial insufficiency of the intestine most commonly is caused by atherosclerosis of two of the three principle arteries supplying the alimentary tract. The syndrome has been reported with other conditions in which arterial blood supply is compromised, such as thromboangiitis obliterans, periarteritis nodosa, polycthemia rubra vera, and progressive arterial occlusive (Kohlmeier-Degos) disease. The dependency of absorptive processes on adequate mesenteric blood supply has been amply demonstrated in animal experiments where the active transport of amino acids and sugars has been shown to be compromised in the face of decreased blood flow to the bowel. While good data are limited, as shown in Table II, any one of several vascular syndromes is capable of producing steatorrhea; generally, the defect is mild and varies from 14 to 26 g per 24 hr. In addition, in atherosclerosis and the Kohlmeier-Degos syndrome very low xylose absorption values, 2.2 ± 0.5 and 1.9 g per 24 hr, respectively, have been reported.

Small bowel resection. In this review, small bowel resection has been divided into three essentially distinct syndromes;: massive resection or bypass, jejunectomy, and ileectomy. As would be anticipated, massive small bowel resection results in severe malabsorption of fat and protein as well as xylose and $B_{12}$ (Table II). In contrast, isolated jejunectomy causes only a mild defect in fat absorption (9 g per 24 hr). Thus, while absorption of major foods normally takes place in the proximal small intestine, in the face of surgical ablation of this area of the intestine, ileal absorption apparently can nearly fully compensate. Paradoxically, resection of the ileum results in severe malabsorption as discussed below under diseases with multiple defects.

Intestinal lymphangiectasis. The basic defect in intestinal lymphangiectasis is considered to be a congenital anomaly of lymphatics with obstruction of intestinal lymphatic outflow which results in loss of lymph containing albumin and chylomicrons into the intestinal lumen. Biopsy reveals dilated intestinal lymphatics containing lipid-laden macrophages. In addition, chylomicrons are present in the intercellular areas, extracellular spaces of the lamina propria, and lymphatics. In this syndrome there is mild steatorrhea (23 ± 4.0 g per 24 hr or 20 ± 3.0% of intake) and a modest elevation of the fecal nitrogen (3.2 ± 1.0 g per 24 hr). However, this latter finding may be a manifestation of the marked protein-losing enteropathy seen in this disease rather than of true protein malabsorption. Xylose absorption is usually normal (7.8 ± 0.5 g per 5 hr).

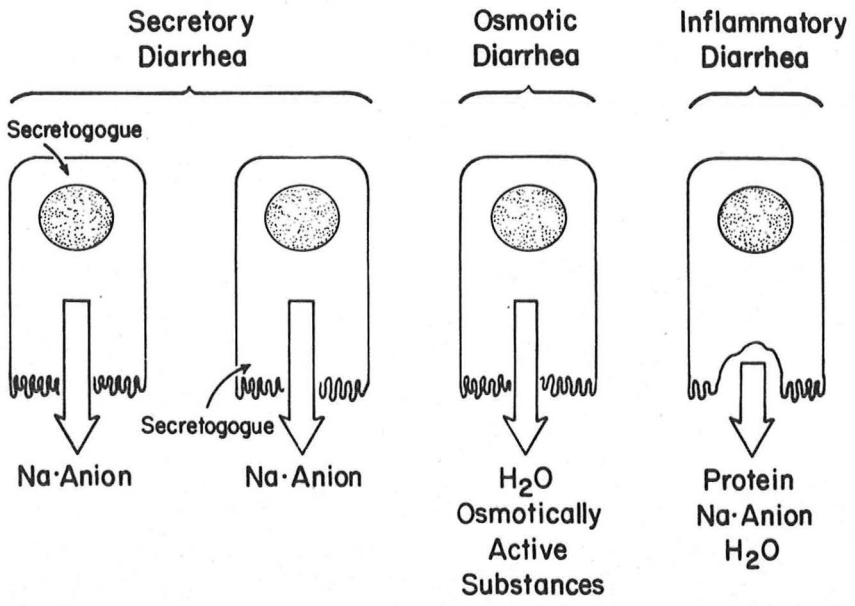
A-β-lipoproteinemia. Steatorrhea and a-β-lipoproteinemia appear to result from inability of the patient to synthesize the protein moiety of the chylomicron; hence, droplets of triglyceride accumulate in the mucosal cell and can be identified in mucosal biopsies of affected individuals even after prolonged fasting. Steatorrhea apparently is mild (18 ± 2.4% of intake) while xylose and $B_{12}$ absorption are perfectly normal as would be anticipated.

Lymphoma. Lymphoma is the most common malignancy producing intestinal malabsorption. Presumably, this tumor results in poor intestinal absorption because of extensive involvement and destruction of the intestinal mucosal and submucosal tissues. Steatorrhea (25 ± 2.8 g per 24 hr or 35 ± 6.9% of intake) and mild azotorrhea (2.4 g per 24 hr) are both present, and there is depressed absorption of both xylose (2.2 ± 0.5 g per 5 hr) and $B_{12}$ (4.0 ± 0.8% per 24 hr).

In summary, this category includes a highly varied collection of diseases that primarily alter intestinal integrity. The specific reason for malabsorption varies depending upon the pathological process. At one extreme are diseases exemplified by gluten enteropathy where the is extensive damage to the absorptive mucosa with severe steatorrhea and azotorrhea as well as depressed absorption of xylose and $B_{12}$. At the other extreme are such diseases as a-β-lipoproteinemia where there is a highly selective defect that impairs only fat absorption so that uptake of other foods and test substances essentially is normal.

Section 7: WORKUP OF OTHER CAUSES OF CHRONIC DIARRHEA

As shown in Fig. 1 the malabsorption of fat and bile acids is not the only cause of chronic bowel dysfunction. There are at least three other major




groups of illnesses that must be considered in any patient presenting with chronic diarrhea. As illustrated in diagrammatic form in Fig. 14 some diseases are manifest by a marked secretory diarrhea. Under these circumstances some portion of the intestine is forced to secrete an isosmotic sodium-anion solution. In these situations these secretogogues may arise from within the intestinal lumen (as, for example, from an enterotoxigenic E. coli infection) or from the bloodstream (from a tumor). In a second group of patients osmotically active substances may reach the lower small intestine and induce net water movement into the intestinal lumen. This results in the production of osmotic diarrhea. Finally, there are a large and diverse group of illnesses that actually result in destruction of epithelial cells within the small and large intestine. This undoubtedly leads to the changes in motility, absorption and secretion that can produce a third form of chronic diarrhea.

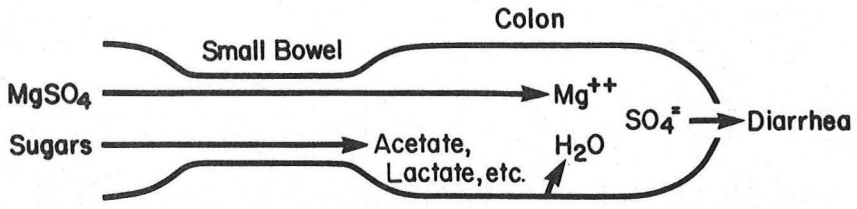
| Stool Weight (g) | Stool Water Osmolality (mOsm/L) | Stool Electrolytes (mEq/L) | Stool pH |
|---|---|---|---|
| <250 (Normal) | 280-300 (Iso-osmotic) | [Na]+[K]>[Cl] | Alkaline |
| 300-1,000 (Osmotic/Inflam.) | <280 (Hypo-osmotic) | | |
| 1,000-15,000 (Secretory) | >300 (Hyper-osmotic) | (2)([Na]+[K]) | Acid |

A) Secretory and Osmotic Diarrheas. In the workup of patients with large volume, watery diarrheas there are essentially four measurements that provide the basis for the differential diagnosis: these include stool weight (or stool volume) per 24 hr, stool water osmolality, the concentration of stool electrolytes and stool pH. As summarized in Fig. 15, normal stool weights are approximately >250 g per 24 hr. Patients with osmotic or inflammatory diarrheas may have stool outputs in the range of 300-1000 g per 24 hr while patients with secretory diarrheas may have much larger volume outputs. Generally, stool water osmolality equals that of plasma (approximately 280-300 mOsm/L). The presence of a grossly hypo-osmotic stool water strongly suggests that the patient has added water to the stool specimen. On the other hand, a hyper-osmotic stool water suggests that the diarrhea is due to the presence of an osmotically active substance in the gastrointestinal tract. The values for stool electrolytes can vary markedly since the relative concentrations of sodium and potassium are a function of how fast the stool moves through the colon. One very important observation is to determine if the observed concentrations of sodium and potassium are enough to account for the observed osmolality, i.e., two times the sum of the sodium and potassium should approximately equal the determined osmolality of the stool water. If the "osmotic gap" is >10 - 15 mOsm/L the patient very likely has an osmotic diarrhea. Finally, in a fresh stool specimen the finding of an acid pH for the stool water strongly suggests that the patient has malabsorption of carbohydrates.

| Measurement | Osmotic Diarrhea (CHO defect, $Mg^{++}$) | Secretory Diarrhea (E.coli, VIP) |
|---|---|---|
| Stool Volume: | 400-1000ml | 1000-4000 ml |
| Effect of 24 hr fast: | Stops | Continues |
| Stool Water: | | |
| Osmolality (mOsm/L) | 350 | 290 |
| [Na] (mEq/L) | 30 | 100 |
| [K] (mEq/L) | 30 | 40 |
| [Na]+[K] (mEq/L) | 60 | 140 |
| (2)(Na+K) | 120 | 280 |
| Osmotic Gap | 230 | 10 |
| pH | acid/alkaline | alkaline |

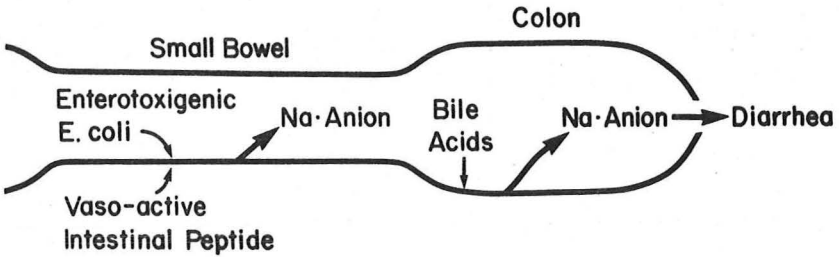
Typical findings in patients with osmotic or secretory diarrheas are summarized in Fig. 16. In patients with osmotic diarrheas the stool volume is commonly between 400-1000 ml and the diarrhea ceases after a 24-48 hr fast. The stool water may be isosmotic but, in some cases, may be hyper-osmotic. Two times the sum of the sodium and potassium concentrations gives a theoretical osmotic pressure that is well below the actual measured value so that there is a large osmotic gap (in this example, 230 mOsm/L). In contrast, secretory diarrheas may have a much larger daily volume and while these volumes decrease with fasting, the diarrhea may persist in the presence of no oral intake. Commonly the stool water is isosmotic with plasma and nearly all of the osmotic pressure can be accounted for by the sodium and potassium (and accompanying negatively charged ions) present in the stool water.

OSMOTIC DIARRHEA




As shown in Fig. 17 osmotic diarrheas can arise for a variety of reasons. Generally, this syndrome is caused by the oral intake of non-absorbable substances or by the generation of osmotically active metabolites of the sugars that are malabsorbed in the proximal small intestine.

SECRETORY DIARRHEA




Secretory diarrheas also can arise for a variety of reasons as illustrated in Fig. 18. The secretogogue may come from a bacterial infection, from a tumor in the systemic tissues or from bile acids reaching the colon. A partial list of the causes of secretory diarrhea is shown in Fig. 19. Often the definitive diagnosis of the specific cause of secretory diarrhea involves studies in which secretory rates are measured in different areas of the intestine and where measurements of circulating hormones (VIP, calcitonin, etc.) are carried out.

## SECRETORY DIARRHEA

A. Intraluminal
   1. Enterotoxin Producing Bacteria
   2. Bile Acid Enteropathy
   3. Ellison-Zollinger

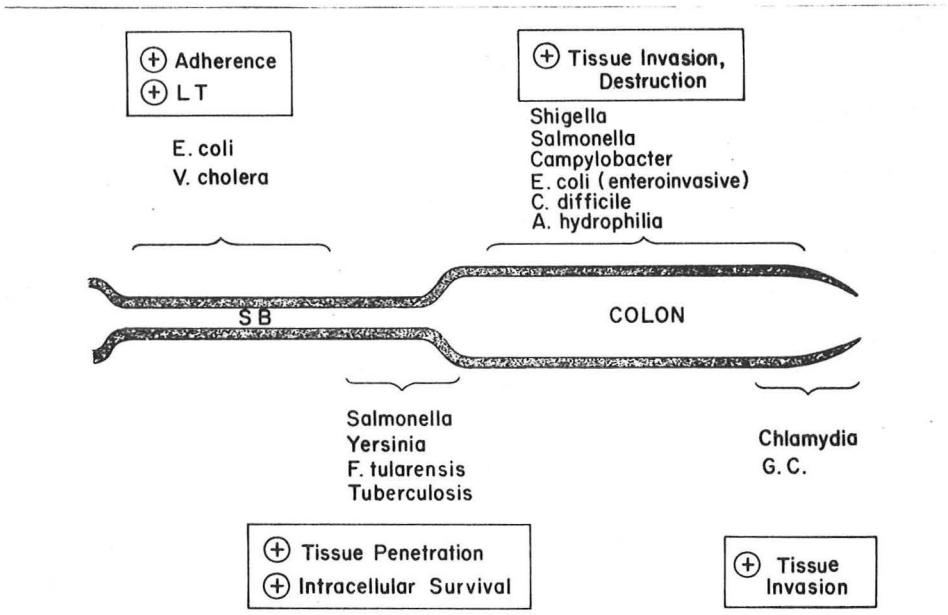
B. Systemic
   1. Prostaglandins (Medullary Ca Thyroid)
   2. VIP (Pancreatic Cholera)
   3. Calcitonin
   4. Diuretics
   5. Carcinoid Syndrome

**DIAGNOSTIC PROCEDURES**

1) Rectosigmoidoscopy (Colonoscopy)
2) Mucosal Smear For WBC
3) Specimens For Bacterial Cultures
4) Scrapings For E. histolytica
5) Barium Enema/Colonoscopy

The major diagnostic procedures that should be carried out in such patients are summarized in Fig. 21. The initial diagnostic procedure that should be undertaken is to subject the patient to rectosigmoidoscopic examination without preliminary preparation of the colon. The purpose of this procedure is to establish that the patient has inflammation of the colon as manifested by erthema, friability, ulceration and exudation. Occasionally some of the diseases that fall into this category (e.g. Crohn's disease or antibiotic associated colitis) will spare the rectum and it will be necessary to perform colonoscopy in order to identify the diseased portion of the colon. During this examination several other diagnostic procedures should be carried out including preparation of a mucosal smear for pus cells, the obtaining of fecal material for bacterial cultures and the obtaining of mucosal scrapings in order to look for E. histolytica in a "warm-stage" preparation. Under circumstances where the disease is more prolonged, it may also be necessary to obtain a barium enema or to perform colonoscopy in order to obtain specific information on the distribution of the inflammatory process in the colon and terminal small bowel. The specimens for bacteriological culture should be taken immediately to the laboratory. The bacteriology laboratory has the capability of culturing pathogenic Shigella, Salmonella, Campylobacter and Yersinia. Most of these organisms can be identified within 24-48 hours: however, Yersinia may require many days or several weeks to grow out. E. coli can also be cultured: however, in order to establish that a particular E. coli is tissue-invasive, and, therefore, the probable cause of acute colitis, would require the performance of a test of tissue invasiveness such as the Sereny test. Such tests are not routinely available in the hospital lab but, in special circumstances, might be performed in one of the research laboratories. C. difficile cannot be cultured routinely in the hospital laboratory: however, the cytotoxin present in stool water of patients infected with this organism can be detected using the tissue culture test discussed earlier (Dr. James Luby, Infectious Disease section).

By following these diagnostic procedures the patient will be identified as having an inflammatory process of the colon. The physician is then faced with the differential diagnosis of a relatively large number of diseases that can produce such "colitis". It should be emphasized that these various illnesses cannot necessarily be distinguished on the basis of clinical behavior, the appearance of the colon or the finding of pus cells in the colonic exudate. Nearly all of the specific diseases that can cause an inflammatory bowel syndrome are capable of producing ulceration, friability and bleeding from the colon and biopsies in nearly all of these illnesses will show inflammatory changes and crypt absesses. The findings that are important in differentiating the various causes of colitis are reviewed in the following three paragraphs.




B. Infectious Diarrheas. As summarized in Fig. 20 there are a number of bacteria that are capable of producing acute and chronic inflammatory bowel disease in the Dallas area. In the small bowel the principal bacterial cause for severe diarrhea would be an infection with an E. coli that is capable of synthesizing an enterotoxin. Organisms such as Salmonella, Yersinia, F. tularensis, Tuberculosis produce an enterocolitis attacking primarily the lymphoid tisssue in the terminal ileum and right colon. Acute and chronic colitis may be produced by infection with Shigella, various tissue invasive Salmonella, Campylobacter, E. coli, C. difficile and A. hydrophilia. Finally, both Chlamydia and G.C. may produce a distal proctitis. In addition to these bacteria, two other parasites are commonly encountered in the Dallas area. These include Giardia and E. histolytica.

Most patients falling into the category of infectious colitis will give a history of frequent, small-volume diarrhea. Not uncommonly a patient will describe the passage of fresh or old blood as well as mucus or pus. The symptoms may vary in duration from only a few days to many months or years depending upon the underlying disease. Commonly there is evidence of tissue invasion/destruction with systemic symptoms, fever and an elevation in the WBC. The illness may vary, however, from a very mild syndrome to one of overwhelming toxicity and death.

| DIAGNOSIS | SUGGESTIVE FINDINGS | DEFINITIVE DIAGNOSIS |
|---|---|---|
| AMOEBIASIS | 1. History of Contaminated Water/Food to Endemic Area<br>2. Duration May be Short or Long<br>3. Isolated Ulcers in "Normal" Mucosa<br>4. Few WBC in Proportion to Degree of Inflammation<br>5. Disease Localized to Cecum or Rectosigmoid Colon<br>6. Prompt Response to Flagyl | 1. Demonstrate E. histolytica<br>2. Elevated CF Test<br>a) Seramoeba Test<br>b) Indirect HA Test |

In this part of the country, amoebiasis is always an important possible cause of colitis. As reviewed in Fig. 22, there are a number of findings that would suggest that this is a possible etiology in a given patient. The patient may have had a history of intake of contaminated water or food or travel to a endemic region such as Mexico, Central America or South America. However, it should be emphasized that amoebiasis can be acquired within the city of Dallas. If sigmoidoscopic examination reveals isolated ulcers in an apparently normal mucosa, amoebiasis should be suspected. However, most cases of amoebiasis have diffuse erythema, ulceration and friability that is indistinguishable from other forms of inflammatory bowel disease. Another observation of importance would be the finding of relatively few pus cells on the mucosal smear when there is clearly marked inflammatory changes in the colon. Nearly all of the other causes of inflammatory colitis will exude large number of WBC's. Finally, the presence of localized disease in the cecum or rectosigmoid colon or a very prompt symptomatic response to Flagyl also suggests amoebiasis. The definitive diagnosis of this disease, however, depends upon either 1) the demonstration of E. histolytica in the stools or mucosal scrapings or 2) a diagnostic elevation of one of the serological tests for amoebiasis. Two such tests are now available at Parkland Hospital: the Seramoeba test and the indirect hemeagglutination test. A negative Seramoeba test is reliable: however, a positive Seramoeba test may represent a false positive and should be confirmed with the indirect hemagglutination test.

| DIAGNOSIS | SUGGESTIVE FINDINGS | DEFINITIVE DIAGNOSIS |
|---|---|---|
| SHIGELLA<br><br>SALMONELLA | 1. History of Contaminated Water/Food Exposure to Sick Individuals<br>2. Self Limited ( < 2 weeks) | Isolate Organism |
| CAMPYLOBACTER | 1. History of Exposure to Animals or Animal Products<br>2. Exascerbation of U.C./C.D.<br>3. Maybe Prolonged to 8 - 10 weeks<br>4. Pseudomembranes | Isolate Organism |
| ENTEROINVASIVE E. coli | 1. History of Contaminated Water/Food Travel to Endemic Area | Isolate Organism and ⊕ Sereny Test |
| C. DIFFICILE | 1. History Antibiotic Intake<br>2. Exascerbation of U.C./C.D.<br>3. May be Prolonged or Recurrent<br>4. Pseudomembranes | Demonstrate Cytotoxin<br>Isolate Organism |
| A. hydrophilia | | Isolate Organism |
| YERSINIA | | Isolate Organism |

As outlined in Fig. 23, there are a number of tissue destructive bacteria that should be considered as potential causes for an inflammatory colitis. Certainly all patients should be cultured for Shigella, Salmonella and Campylobacter. In certain circumstances one may also have to consider the possibility of a tissue invasive E. coli, Yersinia or infection with C. difficile. Patients who have acquired a Shigella or Salmonella commonly give a history of intake of contaminated water or food or exposure to another sick family member or child. Infection with these two organisms is almost always self-limited and virtually never lasts longer than two weeks. Infection with

Campylobacter should be suspected when the history indicates exposure to animals, animal products or unpasturized milk. The disease may be prolonged. Certainly all patients with inflammatory colitis should be carefully questioned with respect to the use of antibiotics. A history of antibiotic intake in the recent past or the finding of pseudomembranes on examination of the colon should immediately raise the possibility that one is dealing with colitis due to overgrowth of C. difficile. The definitive diagnosis of these illnesses will depend upon isolation of a pathogenic Shigella, Salmonella, Campylobacter or Yersinia. Definitive diagnosis of clostridial overgrowth depends upon the demonstration of the cytotoxin in the stool water of such patients.

C. Idiopathic Inflammatory Bowel Disease. The third group of illnesses that must be considered in the differential diagnosis of acute and chronic colitis include the two idiopathic diseases ulcerative colitis and Crohn's disease. There is no definitive way to make either of these diagnoses. Rather, the diagnosis is based upon the presence of a chronic inflammatory reaction with a certain characteristic distribution within the gastrointestinal tract. As discussed in detail above, chronic ulcerative colitis almost always involves the rectum and may involve more proximal portions of the colon as a continuous process. The disease, however, probably never crosses the ileocecal valve to involve the small bowel. Crohn's disease, on the other hand, most commonly involves the terminal ileum and right colon (ileocolitis) or the terminal ileum alone (ileitis). It may involve the colon alone, but when it does so typically involves the right colon, spares the rectum or produces a segmental colitis. In about one-third of the patients one may find granuloma in the submucosal tissue or fistula tracts in various portions of the gastrointestinal tract. Again, it should be emphasized, that these two diagnoses depend upon a demonstrated chronic course and exclusion of all other known forms of colitis.

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