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Normal and Abnormal Intestinal Absorption by Humans

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Adults eating a Western diet digest and absorb ingested food containing approximately 100 g fat, 350 g carbohydrate, and 75 g protein daily. Normal fat absorption requires adequate gastric, pancreatic, liver-biliary, mucosal, and lymphatic function. Carbohydrate and protein absorption is much less dependent on liver-biliary and lymphatic function. The intestine has a large reserve capacity for digestion and absorption of nutrients which is due to both excess function and to adaptive changes which increase function in one segment of the digestive-absorptive system when it is decreased or lost in another segment. The large reserve capacity explains why most of the prevalent intestinal diseases seldom cause clinically detectable changes in absorption. However, there are more than 30 less-common human diseases which cause malabsorption of one or more nutrients. Those that cause the malabsorption syndrome, i.e., steatorrhea and weight loss, can be conveniently categorized according to the major deficiency leading to the absorptive defect as follows: insufficient pancreatic enzyme activity, insufficient bile acid, disease of the small intestinal wall, multiple defects, mechanism unknown, and drug-induced malabsorption. A few diseases, most of which are congenital, cause malabsorption of only one or a few related nutrients such as lactose malabsorption in lactase deficiency. Most of the tests currently in use for detecting and diagnosing the cause of malabsorption are relatively insensitive and nonspecific. Chemical analysis of the fat in a three-day stool collection remains the single best test for diagnosing the malabsorption syndrome. However, a breath test using Triolein labeled with either the radioactive or stable isotope of carbon may be an important recent advance. Other breath tests are also currently being investigated for quantitating absorption or malabsorption of various substances including bile acids and various sugars. Studies of the function of the intestinal epithelial cells are usually best accomplished using tissue obtained by per oral biopsy. Biopsy specimens are used for many types of study including light and electron microscopic examination, chemical and enzymatic assays, tissue culture, and uptake of various radiolabeled compounds.

Absorption of nutrients is the major function of the gastrointestinal system. Although the most prevalent gastrointestinal diseases such as peptic ulcer, cancers, and gallstones seldom cause clinically detectable changes in absorption, there are more than 30 less common human diseases which do cause malabsorption of one or more nutrients (*1, 2*). These diseases and the clinical methods used to evaluate intestinal absorption will be reviewed.

The approximate amounts of various nutrients ingested by normal adult Americans is shown in Table 1 (*3*). In addition, endogenous secretions must be digested and absorbed, and they contribute about 6500 ml of water, 35 to 100 g protein, and possibly 20 to 30 g fat each day.

Table 2 summarizes the steps in digestion and absorption of fats, carbohydrates and proteins. For the sake of brevity, important gastric functions are not shown. Pancreatic lipase assisted by colipase, a low molecular weight protein which is also secreted by the pancreas, hydrolyzes ingested triglyceride predominantly to free fatty acids and β-monoglyceride (*4*). This mixture is solubilized to a clear micellar solution by the action of bile acids (*5, 6*). The fatty acids and β-monoglyceride diffuse from the micelles into the intestinal mucosa while bile acids remain in the lumen and are absorbed by an active process in the terminal ileum (*7*). Within the mucosal cell, triglyceride is resynthesized and packaged with cholesterol, cholesterol esters, and specific proteins to form chylomicrons which leave the baso-lateral membrane of the cell, enter lymphatics, and eventually join the blood via the thoracic duct (*8, 9*). Digestion and absorption of carbohydrates and proteins is less complex (*8*). Pancreatic amylase hydrolyzes

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Table 1. Typical Daily Intake (2600 calories).

Food	Amount	Form
Fat	100 g	95% triglycerides 5% other
Carbohydrates	350 g	50% starch 35% disaccharides 10% monosaccharides 5% fiber
Protein	75 g	mixed proteins
Other	few g	vitamins, minerals
Water	2300 ml	

starch only to maltose and small oligosaccharides (*10*). These products plus ingested disaccharides, primarily lactose and sucrose, are further cleaved to monosaccharides by disaccharidases in the brush border membrane of the epithelial cells. In contrast, approximately ⅓ to ½ of the ingested protein is hydrolyzed completely to free amino acids by pancreatic enzymes. What remains is peptides averaging 2 to 6 amino acids in length which are cleaved by peptide hydrolases while being transported through the epithelial cells. Peptide hydrolases are present not only in the brush border membrane but also in the cytosol and it is clear that some peptide molecules are transported intact and hydrolyzed inside the cell (*11*).

The quantities of nutrients ingested (Table 1) are far less than the digestive-absorptive capacity of the intestine. Although fecal fat does increase slightly with increasing amounts of fat ingested, normal subjects are capable of absorbing more than 350 g of fat daily (*12*). The reserve capacity for carbohydrate and protein is even greater than for fat. Reserve capacity is in part due to excess function, including 9- to 10-fold more pancreatic enzyme activity (*13*), 2- to 3-fold higher bile salt concentration (*2, 7*), and severalfold more surface area, at least for protein and carbohydrate (*14*), than the minimum required for normal absorption. Adaptation also contributes to the reserve capacity of the intestine. Thus, following resection or by-pass of part of the small intestine the remaining segment undergoes changes in enzyme activity and morphology and an increase in absorbing capacity per centimeter of length (*15, 16*). Also, resection or disease of the terminal ileum which results in excessive fecal losses of bile acids induces an increase in bile acid synthesis by the liver of up to 10-fold the normal rate (*7*). The digestive system can also partially compensate for total loss of pancreatic secretions (*17, 18*). Although this reserve absorptive capacity is of obvious benefit it often precludes early detection of conditions that cause malabsorption or detection of slight damage.

The malabsorption syndrome, i.e., steatorrhea and weight loss, is caused by many diseases which can be conveniently divided into groups based on the major deficiency leading to the absorptive defect (Table 3) (*1, 2*). Most of these diseases cause malabsorption of many or all nutrients. There are other diseases which cause malabsorption of only one or a few related nutrients and which do not produce the malabsorption syndrome. The most important of these are categorized in Table 4 (*19*).

Although a great many tests have been proposed for detecting and diagnosing the cause of malabsorption, many of them are only different methods of gathering the same information. Therefore, a rational approach to investigation of suspected malabsorption need not involve a large number of tests. By history, most patients with malabsorption have diarrhea and weight loss, but occasionally the patient will complain predominantly of one or more other

Table 2. Steps in digestion and absorption of fats.

	Intestinal lumen		Epithelial cell			
	Pancreas	Liver	Brush border	Cytosol	Lymphatics	Blood
	Digestion	Micellar solubilization	Digestion-absorption			
Triglycerides →	fatty acids + β-monoglyceride	→ mixed micelles →	absorption →	triglycerides then chylomicrons →	→	
Carbohydrates						
Starch →	oligosaccharides + disaccharides	→	monosaccharides →			
Disaccharides		→	monosaccharides →			
Protein →	oligopeptides + amino acids	→	amino acids			

Table 3. Diseases which cause the malabsorption syndrome.

Insufficient pancreatic enzyme activity
Chronic pancreatitis
Pancreatic carcinoma
Pancreatic resection
Cystic fibrosis
Enterokinase deficiency
Isolated lipase deficiency
Insufficient bile acid
Extrahepatic biliary obstruction
Intrahepatic biliary obstruction
Intestinal stasis syndromes
Disease of the small intestinal wall
Celiac sprue
Tropical sprue
Whipple's disease
Infiltrative disease—amyloid, lymphoma
Small bowel ischemia — athrosclerosis, vasculitis
Jejunal resection
Intestinal lymphangiectasia
a-B-Lipoproteinemia
Multiple defects
Gastrin-secreting tumor
Scleroderma
Ileal dysfunction — resection, disease
Steatorrhea following gastric surgery
Radiation enteritis
Mechanism unknown
Mast cell disease
Immune deficiencies
Carcinoid
Diabetes mellitus
Hyperthyroidism
Adrenal insufficiency
Parasitic infections (giardiasis, strongyloidiasis)
Drugs
Colchicine
Cholestyramine
p-Aminosalicylate
Cathartics
Neomycin
Alcohol
Clofibrate
Phenindione

symptoms including weakness, bleeding tendency, sore tongue, tetany, bone pain, edema, amenorrhea, or peripheral neuritis. The physical exam is often unremarkable but may show signs of malnutrition or of specific vitamin deficiencies.

Since most patients who present with these symptoms and signs will not have malabsorption, appropriate tests must be done to rule out the other more common conditions including intestinal cancers, inflammatory bowel disease, and infectious diarrheas.

Initial procedures to investigate malabsorption generally include visual inspection of the stool, examination of the stool for meat fibers (*20*), and semiquantitative determination of fecal fat by counting microscopic lipid droplets after treatment of a stool specimen with a fat stain such as sudan (*20, 21*). Initial blood studies include carotenoids and folic acid. Since these compounds are not synthesized or stored by humans in appreciable quantities, the blood levels fall when absorption decreases if intake remains constant. However, low folate and carotenoid levels are not specific for malabsorption. Prothrombin time or serum alkaline phosphatase activity may be abnormal when vitamin K or vitamin D and calcium absorption, respectively, have been decreased for a long period of time. Blood levels of calcium, magnesium, phosphorus, cholesterol, and vitamin B_{12} may also be obtained, but the results are often normal or only slightly decreased even when malabsorption is clinically obvious. Plain radiographs of the abdomen and barium contrast studies of the upper gastrointestinal tract and small bowel are performed to look for evidence of pancreatic or small bowel disease.

Since the digestion-absorption of fat requires more steps and has less reserve capacity than that for other nutrients, quantitative analysis of stool fat in a 72-hr collection is the most definitive test for malabsorption. The patient must be ingesting a known quantity of fat, greater than 50 g/day and preferably close to 100 g/day, beginning at least 48 hr before starting the collection. Accuracy of the test depends on careful stool collection and estimation of fat intake, avoidance of drugs that alter intestinal motility, barium, or other agents that interfere with the assay and cathartics or other suppositories that add fat to the stool, and a properly performed assay.

Table 4. Diseases which cause malabsorption of only one or a few related nutrients.

Primary disaccharidase deficiency
Acquired lactase deficiency
Congenital lactase deficiency
Congenital sucrase-isomaltase deficiency
Monosaccharide malabsorption
Glucose malabsorption
Fructose malabsorption
Amino acid malabsorption
Cystinuria
Hartnup's disease
Methionine malabsorption
Proline malabsorption
Vitamin B_{12} malabsorption
Pernicious anemia
Congenital B_{12} malabsorption
Alcohol
Folic acid malabsorption
Oral contraceptives
Dilatin
Alcohol

Recently a promising new test for fat malabsorption has been developed, namely the ^{14}C-triolein breath test (*22*). Triolein labeled with ^{14}C in the carboxyl group is given orally, and the percent of administered label expired as $^{14}CO_2$ over the next 6 hr is determined. Constant collection of the expired CO_2 is possible but impractical. Instead a known quantity of the CO_2 is collected in hyamine at intervals and its specific activity is determined by scintillation counting. The total label expired in 6 hr is then calculated by assuming a constant CO_2 production of 9 mmole/kg-hr for the patient at rest. The initial report (*22*) which indicates that this test is as sensitive and specific for fat malabsorption as the 72-hr fecal fat assay requires confirmation. The breath test can also be done by using ^{13}C-triolein, avoiding a radioactive label (*23*).

The D-xylose test is frequently used in evaluating intestinal absorption (*24, 25*). D-Xylose is a five-carbon sugar that is absorbed by the intestinal mucosa and requires no intraluminal digestion. It is poorly metabolized in the body and is excreted intact in the urine. After an oral dose, urine is collected for 5 hr and assayed colorimetrically for D-xylose. Normally, 20% or more of the ingested dose is present in this urine specimen. Determination of blood levels of D-xylose 30 to 60 min following the dose may add significantly to the accuracy of the test. Lower levels suggest a decrease in effective mucosal surface area or intestinal stasis in which bacteria metabolize the D-xylose before it can be absorbed. There are many causes of falsely low test results and occasional patients with documented mucosal disease have normal test results. For these reasons the test may eventually fall into disuse in favor of proceeding directly to peroral intestinal biopsy for evaluating the intestinal mucosa (*26*).

Peroral biopsy of the intestinal mucosa is a safe, relatively simple procedure (*27*). Depending on the instrument used, one to four pieces of tissue can be obtained with a total weight of up to approximately 35 mg. A hydraulic instrument is available for research purposes which will permit repeated biopsies from the same patient at different levels of the small intestine without having to repeatedly remove and re-insert the instrument (*28*). Biopsy specimens are used for many types of study including light and electron microscopic examination, chemical and enzymatic assays, tissue culture, and uptake of various radiolabeled compounds.

There are a few other useful tests of intestinal function. Pancreatic secretory tests are used in which a tube is passed by mouth into the duodenum whereby secretions from the pancreas can be aspirated. The pancreas is then stimulated to secrete either by injecting the hormone secretin or by giving a standard meal and the volume, composition, and enzyme activity of the secreted pancreatic fluid is measured and compared with established normal values (*29*). The Schilling test determines B_{12} absorption by measurement of radiolabeled B_{12} excreted in the urine for 24 hr following an oral dose (*30*). A large dose of nonlabeled vitamin is given parenterally to saturate tissue-binding sites. Intrinsic factor normally secreted by the stomach is necessary for B_{12} absorption so if the initial (first stage) test is abnormal the test must be repeated, this time giving intrinsic factor with the oral B_{12} (second stage). An abnormal second stage test indicates either dysfunction of the terminal ileum, where B_{12} is actively absorbed, or intestinal stasis as the bacteria in this condition may take up and bind B_{12} before it can be absorbed.

Excessive loss of whole protein from the intestine can be measured by giving ^{51}Cr albumin intravenously and measuring fecal radioactivity for several days. Chromium is practically nonabsorbable, so any that leaks out into the intestinal lumen attached to albumin will remain and be passed in the stool even though the protein is digested and absorbed (*31*).

Breath tests similar to the triolein test already described have been reported for detecting malabsorption or metabolism of other compounds labeled with ^{13}C or ^{14}C including bile acids, D-xylose, and aminopyrine (*32-34*). When the bile acid cholylglycine labeled with ^{14}C in the glycine moiety is given orally to normal subjects most of the compound is absorbed intact in the terminal ileum and enters the enterohepatic circulation so relatively little is metabolized. If the bile acid comes in contact with a large population of anerobic bacteria deconjugation may occur, and the released glycine is metabolized to $^{14}CO_2$ which is absorbed by the intestine and expired in the breath. Thus, either ileal dysfunction, which causes the bile acid to escape into the colon in excess quantities, or intestinal stasis in which colonic type bacteria overgrow in the upper intestine will cause excessive quantitites of $^{14}CO_2$ to be expired following administration of the labeled bile acid. The two conditions can be distinguished by measuring fecal radioactivity, which is elevated in the case of ileal dysfunction but not in intestinal stasis.

Finally, several new, apparently useful tests for malabsorption of various carbohydrates make use of measurement of hydrogen in the breath following ingestion of the test carbohydrate (*35, 36*). Bacteria, but not mammalian cells, produce hydrogen during metabolism of sugars. Hydrogen produced in the

intestinal lumen by bacteria is readily absorbed from the intestinal tract and expired in the breath. Therefore, the presence of significant amounts of hydrogen in the breath following ingestion of any carbohydrate indicates that bacteria are coming in contact with the compound. Normally, ordinary doses of compounds such as lactose, sucrose, and glucose are 100% absorbed. Therefore, increased breath hydrogen following their ingestion indicates malabsorption or bacterial overgrowth in the upper intestine. On the other hand, lactulose is a sugar that is not absorbed by humans, so that the time of appearance of hydrogen in the breath following its ingestion has been used to measure intestinal transit time as well as bacterial overgrowth.

In summary, although absorption is the main function of the intestine the system has a large reserve capacity so that most of the tests currently used are not likely to detect early or mild changes. Measurements done on peroral intestinal biopsies and possibly some of the developing breath tests offer more senstive methods for detecting intestinal dysfunction.

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