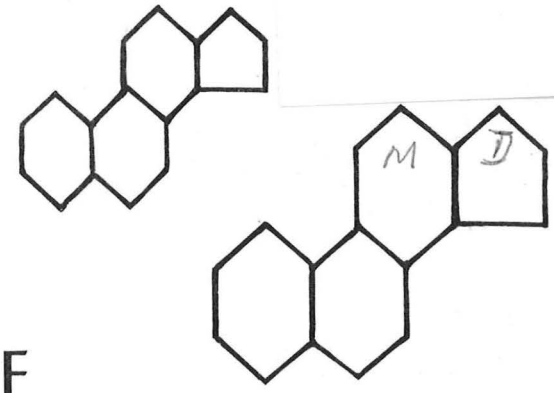
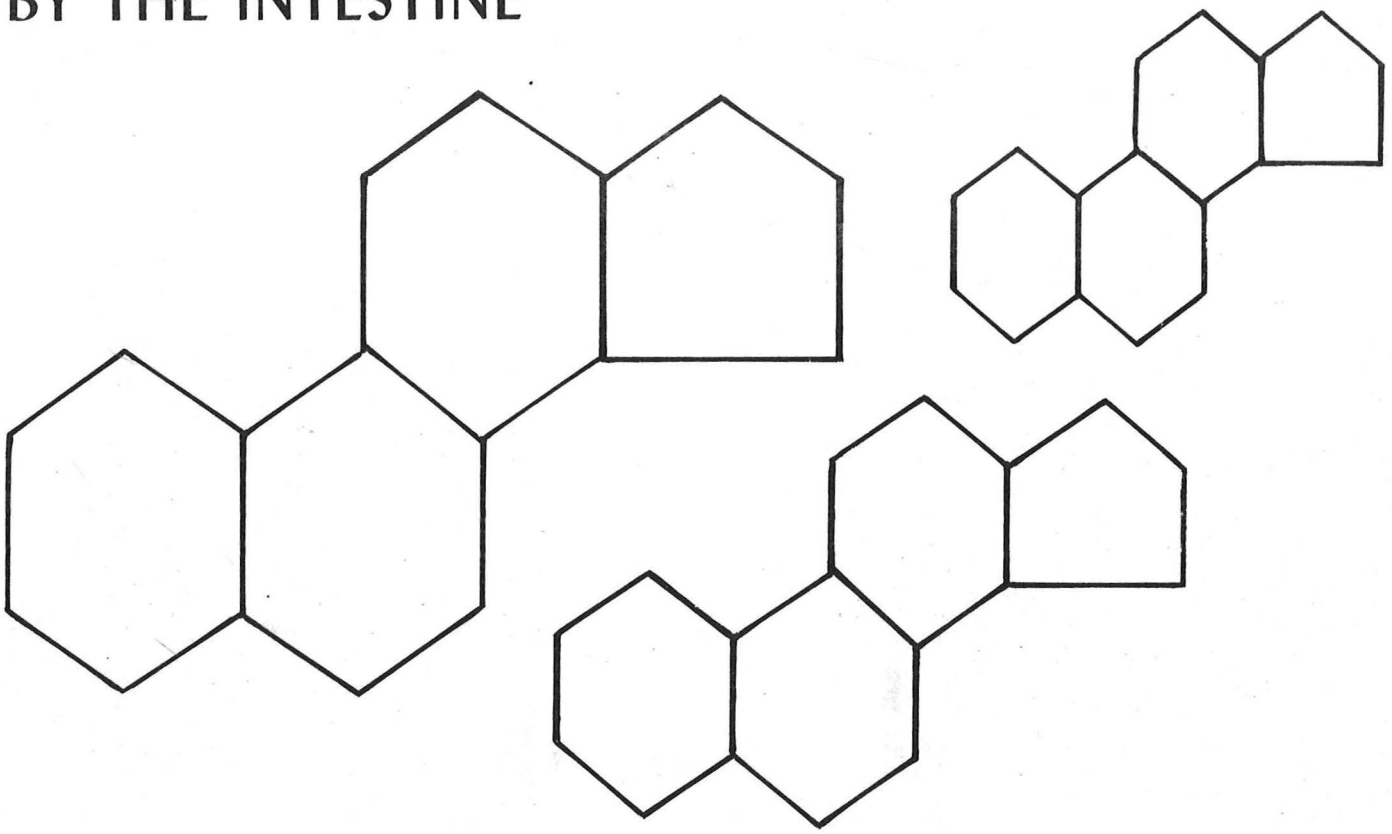
July, 1976

MEDICAL GRAND ROUNDS



DISEASES ASSOCIATED WITH DISORDERED PHYSIOLOGY OF THE ENTEROHEPATIC CIRCULATION OF BILE ACIDS AND OF FAT ABSORPTION BY THE INTESTINE



- Normal Physiology of Fat Absorption
- Diseases of Fat Malabsorption
- Diseases of Disordered Bile Acid Metabolism

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TABLE OF CONTENTS

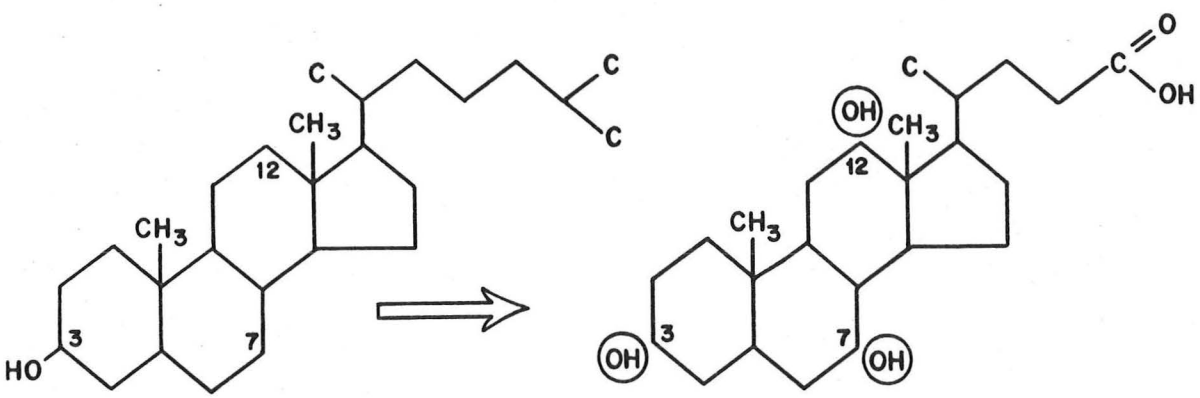
I. PHYSIOLOGY AND CHEMISTRY OF BILE ACIDS

Bile acids constitute one of the major degradative products of cholesterol metabolism and play a critical role in the body in three general areas: 1) formation of bile acids represents one of the two major pathways for the ultimate excretion of the sterol nucleus from the body, 2) bile acids act at the bile-cannicular membrane interface to solubilize cholesterol being secreted from the hepatocyte and 3) bile acids act in the intestinal lumen to solubilize various dietary lipids and promote their absorption.

As shown diagrammatically in Fig. I-1, three important biochemical modifications occur in the liver as cholesterol is converted to cholanic acid. First, the three terminal carbon atoms on the 8 carbon side chain of cholesterol is cleaved thus converting a 27-carbon sterol (cholesterol) to the 24-carbon configuration typical of human bile acid (cholanic acid). Second, the C-24 carbon is oxidized to an acid function that has a relatively high pKa of approximately 6.5. Third, the unsaturated bond in cholesterol is saturated and the configuration of the A and B rings is converted from the *trans* to the *cis* configuration, i.e., cholesterol is a 5α-sterol while most naturally occurring bile acids are 5β-sterols. In addition to these three structural changes a variable number of hydroxyl groups are added to the sterol nucleus and, in man, these additions usually occur in the α-configuration at the 3, 7 or 12 positions. As listed in Table I-1, the liver predominantly synthesizes two bile acids directly from cholesterol: hence, these two bile acids are referred to as *primary* bile acids. These include cholic acid which has hydroxyl groups in the 3, 7 and 12 positions and chenic (chenodeoxycholic) acid which has hydroxyl groups in the 3 and 7 positions. In the terminal gastrointestinal tract bacteria are present which contain 7-dehydroxylase enzymes capable of removing the hydroxyl group in the 7 position on these two primary bile acids. As a consequence, a series of *secondary* bile acids are formed. Cholic acid is dehydroxylated to form the 3,12 dihydroxy bile acid deoxycholic acid. Chenic acid is dehydroxylated to form the 3-monohydroxy bile acid lithocholic acid. In addition, a portion of the formed lithocholic acid may be absorbed from the gastrointestinal tract and sulfated at the 3 position to form lithocholic acid sulfate.

In the body these bile acids are never secreted by the liver into the bile as the free acid. Since the pKa for the carboxyl function on the free acids is so close to neutrality these bile acids have very limited solubility and are poor micelle-forming agents. Rather, prior to secretion from the hepatocyte all of these various bile acids are first conjugated through the C-24 carbon to either taurine or glycine. This results in compounds that are much more acidic (glycine conjugates, pKa - 3.5, taurine conjugates, pKa - 1.5) and more soluble in aqueous solution. Hence, as listed in Table I-2, in human bile one finds a complex mixture of the taurine and glycine conjugates of the five primary and secondary bile acids listed in Table I-1. Of these various conjugated bile acids human bile contains principally the taurine and glycine conjugates of cholic acid, chenic acid and deoxycholic acid.

All of these various bile acids are secreted from the liver into the gastrointestinal tract, are absorbed to varying degrees by passive



Cholesterol (C-27)

Cholanic Acid (C-24)

Fig. I-1. Biochemical modifications of the cholesterol molecule during formation of bile acids.

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mechanisms in the proximal small intestine and by active transport mechanisms in the distal small intestine and are returned to the liver in the portal blood. Thus, all of the various chemical species of bile acids participate in the enterohepatic circulation. However, there are a number of differences in the rates at which these various types of bile acids are reabsorbed from the gastrointestinal tract, and, hence, their average life time in the enterohepatic circulation varies. It is now apparent from a variety of studies that bile acids are absorbed by both passive and active transport mechanisms. In general, the more polar trihydroxy bile acids are absorbed at only very low rates by passive mechanisms but at high rates by active transport mechanisms localized to the ileum. In contrast, the less polar, dihydroxy and monohydroxy bile acids are absorbed relatively rapidly by passive mechanisms but more slowly by the active transport sites present in the distal small bowel. These differences are illustrated in quantitative terms in Table I-3 where the passive and active transport rates are illustrated for a variety of bile acids in rat intestine.

TABLE I-1. PRINCIPAL UNCONJUGATED BILE ACIDS IN MAN

Primary Bile Acids	Secondary Bile Acids
Cholic Acid (3,7, 12 tri OH)	Deoxycholic Acid (3,12 di OH)
Chenic Acid (3,7 di OH)	Lithocholic Acid (3 monoOH)
	Lithocholic Acid Sulfate

TABLE II-2. PRINCIPAL CONJUGATED BILE ACIDS IN MAN

Primary Bile Acids	Secondary Bile Acids
Taurocholic Acid	Taurodoexycholic Acid
Glycocholic Acid	Glycodeoxcholic Acid
Taurochenic Acid	Taurolithocholic Acid
Glycochenic Acid	Glycolithocholic Acid
	Taurolithocholic Acid Sulfate
	Glycolithocholic Acid Sulfate

TABLE I-3. RATES OF ACTIVE AND PASSIVE TRANSPORT

Bile Acid	Rate Active Transport	Rate Passive Transport
C	1906	254
GC	1543	51
TC	1629	39
DC	224	1237
GDC	114	133
TDC	397	114
CDC	512	974
GCDC	173	142
TCDC	337	138
GLC	45	429
TLC	57	387

This table shows the relative rates of active transport (V_{max}) and passive transport (passive permeability coefficients) for a variety of bile acids tested in the gut of the rat.

As a consequence of these differences in absorption rates, the kinetic characteristics of each bile acid vary in the enterohepatic circulation of man. These kinetic characteristics for the major bile acids are summarized in Table I-4. As is apparent, cholic acid has the largest pool size (600-1000 mg)

TABLE I-4. BILE ACID KINETICS IN HEALTHY MAN

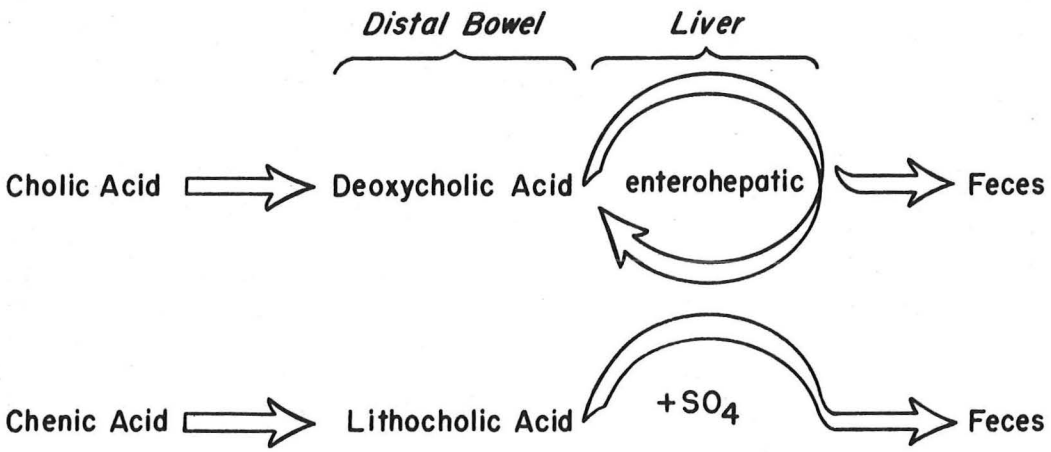
Type of Bile Acid	Pool	Turnover each day	Daily Synthesis or Input
	mg		*mg*
Cholic	600-1,000	0.32	192-320
Deoxycholic	200-400	0.20	40-80
Chenic	500-800	0.20	100-160
Lithocholic	40-80	1.0	40-80
Total	1,340-2,280		

(From Hofmann, 1976)

and the highest daily synthetic rate (192-320 mg). Each day approximately 32% of the pool is turned over. The two dihydroxy bile acids are more readily retained in the enterohepatic circulation so that only 20% of the pool of these two acids is turned over each day. The least common bile acid in human bile is lithocholic acid. This material is potentially hepatotoxic and, as outlined above, is not only conjugated but is sulfated during passage through the liver. As a consequence, intestinal reabsorption is greatly diminished so that little lithocholic acid is retained in the enterohepatic circulation and the total pool is essentially excreted each day (Fig. I-2).

In the normal individual, then, the enterohepatic circulation continually circulates a relatively small pool of bile acid approximately 6 to 8 times per day. Thus, a bile acid pool of approximately 3 gm circulated 6 times would lead to a bile acid secretory rate from the liver of 18 gm. Hence, the effect of a relatively small pool of bile acid is greatly amplified by the presence of an intact enterohepatic circulation. Any interruption of this enterohepatic circulation seriously compromises the physiological effects of bile acid in the body.

Fig. I-2



II. NORMAL MECHANISMS OF FAT AND CHOLESTEROL ABSORPTION

The general features of normal fat and cholesterol absorption are shown in a simplified fashion in Fig. II-1. The average western diet contains approximately 60 to 100 gm of triglyceride lipids and 0.5 to 1.0 gm of cholesterol each day. After ingestion, little hydrolysis occurs in the stomach; in the proximal small intestine, however, the triglyceride and cholesterol esters of the diet come under hydrolytic attack by pancreatic esterases. A pancreatic lipase splits the triglyceride molecule into free fatty acids and β-monoglycerides while a pancreatic cholesterol ester esterase hydrolyzes dietary cholesterol esters. The products of lipolysis are then solubilized in the bile acid micelle and carried to the microvillus border of the jejunal absorptive cell. There the fatty acids, β-monoglycerides and free cholesterol diffuse passively across the brush border membrane and enter the cytosolic compartment of the columnar cell. Within the cell the majority of the free cholesterol is immediately reesterified to long chain fatty acids and nearly all of the free fatty acids and β-monoglycerides also are reesterified to triglyceride. This triglyceride along with the lesser amounts of cholesterol and other lipid-soluble materials absorbed from the diet are incorporated into a specific lipoprotein fraction, the chylomicron. This particle is extruded from the base of the columnar epithelial cell and enters the central lacteal of the intestinal villus. It then travels through the intestinal lymphatics of the thoracic duct and, eventually, enters the circulation where much of the triglyceride is delivered to the peripheral tissues for utilization while the cholesterol moiety is selectively taken up by the liver. A more detailed description of the specific events occuring in the process of normal fat and sterol absorption are outlined in Fig. II-2 and described below.

A. Pancreatic Phase

After ingestion of a meal, little lipolysis takes place in the stomach although lipase activity has been described in glands situated at the base of the tongue and in the stomach. Rather, in the stomach the ingested lipids are partially emulsified and then delivered into the duodenum. The presence of fat in the duodenum causes the release of various hormones from the duodenal mucosa which, in turn, causes the gallbladder to contract and stimulate the pancreas to secrete enzymes and bicarbonate. The major pancreatic enzymes involved in lipolysis include triglyceride lipase which attacks the glycerol-fatty acid ester bonds in the 1 and 3 positions and results in the release of β-monoglycerides and fatty acid; cholesterol ester esterase which hydrolyzes cholesterol esters to free cholesterol and fatty acids; and phospholipase which converts lecithin to lysolecithin and fatty acid. The lipolytic enzymes attack the emulsified particles of diet at the oil-water interface, and the products of lipolysis are released into the aqueous enviroment. However, the solubility of these products is very low in water; for example, the solubility of saturated long chain fatty acids has been estimated to be of the order of 5 to 10 x 10^{-6} M, and cholesterol is even less soluble. Thus, even though extensive hydrolysis of dietary lipids occurs under the influence of pancreatic enzymes only small amounts of the resulting fatty acids, β-monoglyceride and cholesterol could be dissolved in the aqueous phase if bile acids were not present.

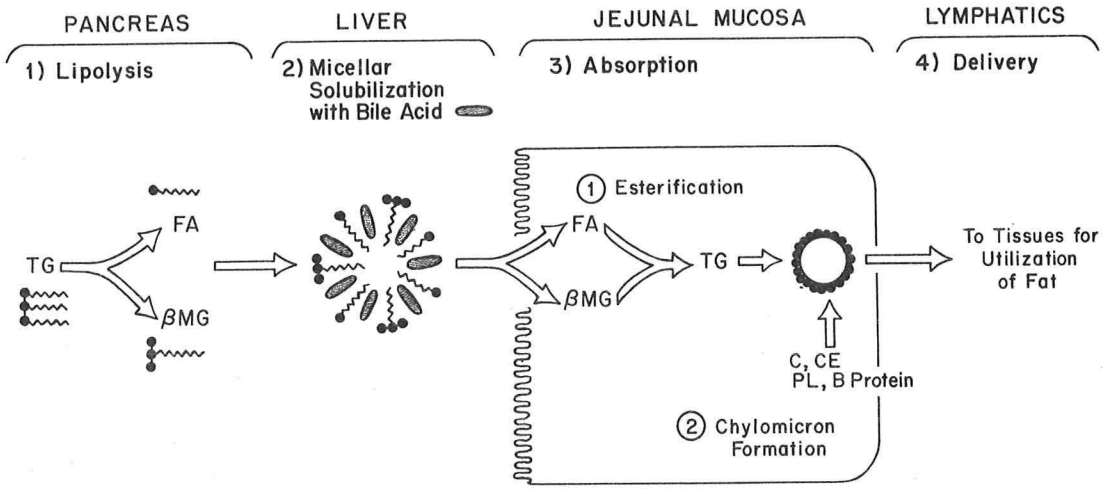


FIG. II-1. Diagrammatic representation of the major steps in the digestion and absorption of dietary fat. These include: (1) the lipolysis of dietary triglyceride (TG) by pancreatic enzymes; (2) micellar solubilization of the resulting long chain fatty acids (FA) and β-monoglycerides (βMG) by bile acids secreted into the intestinal lumen by the liver; (3) absorption of the fatty acids and β-monoglyceride into the mucosal cell with subsequent reesterification and formation of chylomicrons; and finally, (4) movement of the chylomicrons from the mucosal cell into the intestinal lymphatic system. During the process of chylomicron formation small amounts of cholesterol (C), cholesterol ester (CE), and phospholipid (PL) as well as triglyceride are incorporated into this specific lipoprotein fraction.

B. Micellar Solubilization Phase

When the gallbladder contracts during a meal the bile acid pool is transferred to the proximal small intestine where a relatively high concentration of bile acid is achieved in the jejunal contents. In studies in man, during a meal bile acid concentrations in the proximal small intestine are found to be in the range of 3 to 6 mM which is well above the critical micelle concentration. Thus, a solution with a high solubilizing capacity for the products of lipolysis is present in the jejunum during the initial stages of fat digestion. The long chain fatty acid and cholesterol solubilized in this aqueous solution is partitioned in such a way that a portion

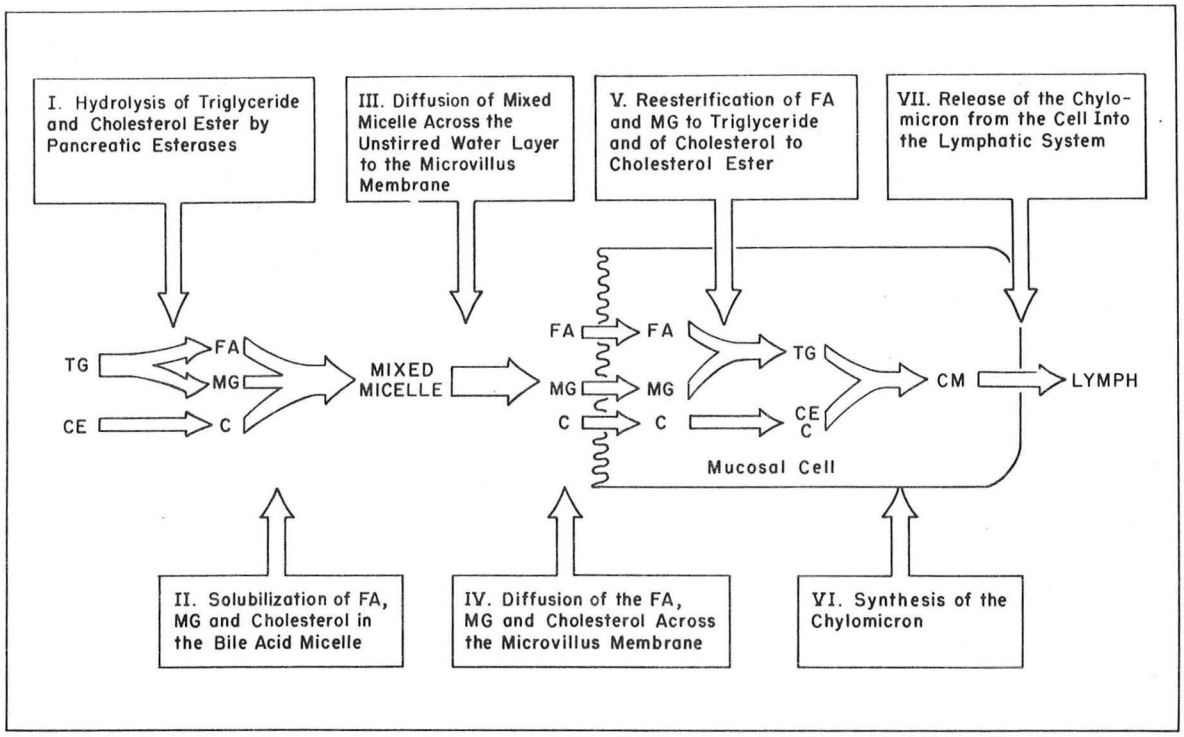


FIG. II-2. Diagrammatic representation of the major steps involved in the digestion and absorption of dietary triglycerides and cholesterol esters. In this illustration the following abbreviations are used: triglyceride (TG), cholesterol esters (CE), unesterified cholesterol (C), long chain fatty acids (FA), β-monoglycerides (MG) and chylomicrons (CM).

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of each compound is in solution in the water phase while the remainder is dissolved in the bile acid micelle. The amount of the particular lipid solubilized in these two phases is dictated by the micelle-water partitioning coefficients for that substance. In general, such coefficients vary inversely with a compound's relative polarity and solubility in water. Thus, medium chain length fatty acids, i.e., fatty acids with chain lengths of 8 to 14 carbon atoms, are relatively polar compounds with relatively high water solubility and low micelle:water partitioning coefficients. Such fatty acids are predominantly solubilized in the water phase of the intestinal contents and, therefore, do not require bile acid micelles for solubilization. In contrast, saturated and unsaturated long chain fatty acids and cholesterol are much less polar and so have micelle:water partitioning coefficients that are very much higher; hence, greater than 96 to 99 per cent of long chain fatty acid or sterol solubilized in intestinal contents will be present in the bile acid micelle rather that in solution in the aqueous phase. The small but finite amount of fatty acid and sterol dissolved in the water phase

is in dynamic equilibrium with the lipids in the micelle so that there is constant exchange between molecules in the water and micellar phases.

Once micellar solubilization is complete the mixed micelle diffuses towards the intestinal epithelial cell. It has been known for many years that immediately adjacent to all biological membranes there are layers of water which are relatively unstirred and through which diffusion is the only mechanism of molecular movement. The effective thickness of this layer depends primarily upon the degree of mixing of the bulk solution perfusing the membrane: in the case of the intestine the thickness of this layer presumably depends on the degree of mixing of the intestinal contents. In several *in vitro* systems with different biological membranes the unstirred water layer has been estimated to be approximately 100 to 400 μm thick, but it is probably much thicker *in vivo*. Thus, in effect, as a molecule moves from the bulk intestinal contents into the mucosal cell interior it must cross two membranes in series: an unstirred layer of water and the lipid-protein membrane of the microvilli.

In steady state the rate of movement, J, of a given molecule across these two membranes is given by the equation

$$J = (C_1 - C_2)\left(\frac{D}{d}\right) = P(C_2 - C_3)$$

where C_1, C_2 and C_3 are the concentrations of the compound in the bulk solution, at the aqueous-lipid interface and in the cell interior, respectively, D is the free diffusion coefficient for the molecule; d is the thickness of the unstirred water layer; and P is the passive permeability coefficient of the cell membrane. The term D/d can be viewed as the permeability coefficient of the unstirred "water" membrane while P is the permeability coefficient for the "lipid" membrane. For the movement of a molecule from the bulk intestinal contents into the interior of the mucosal cell two extreme situations may exist: either D/d may be very much larger than P in which case the rate of movement across the cell membrane is rate limiting to absorption or, alternatively, P may be very much larger than D/d in which case the rate of diffusion across the unstirred water layer is rate limiting to cellular uptake.

Recent work has demonstrated that long chain fatty acids and sterols are able to penetrate the microvillus membrane at very rapid rates, i.e., these compounds have very high passive permeability coefficients, P. As a consequence the important observation has been made that for these compounds P is very much larger than D/d so that the unstirred water layer, and not the cell membrane, is rate limiting to mucosal cell uptake. Stated in another way, the major resistance to the absorption of cholesterol, β-monoglycerides, and fatty acids is the aqueous diffusion barrier.

The precise function of the bile acid micelle, therefore, in facilitating lipid absorption must be defined in terms of overcoming this unstirred resistance. This is accomplished by formation of the mixed micelle in the bulk intestinal contents and diffusion of this particle across the unstirred water layer to the region of the aqueous-lipid interface at the microvillus border. Since the micelle can solubilize a very large amount of fatty acid, monoglyceride and sterol and since the diffusivity of the mixed micelle

particle is reduced only in proportion to the cube root of its molecular weight, the net effect is that there is much more rapid transfer of the end products of lipolysis across the unstirred water layer in the presence of a bile acid micelle than in the absence of this structure.

C. Mucosal Uptake Phase

Once the micelle has carried the fatty acid, monoglyceride and cholesterol across the unstirred water layer, actual absorption takes place as these lipids move into the intestinal mucosal cell. The process responsible for this uptake step has been poorly understood until recently. All current experimental evidence indicates that the actual translocation step is a passive process. Thus, the rate of movement, J, of a given compound across the microvillus membrane must be determined by its concentration at the interface, C_2, times its appropriate permeability coefficient, P. However, since the lipolytic products exist in two phases in the aqueous solution at the membrane interface, i.e., dissolved as a monomer in the aqueous phase and carried in the structure of the bile acid micelle, at least two different mechanisms exist to explain events during the uptake step. It has been suggested, for example, that the bile acid micelle interacts with, or binds to, the microvillus membrane following which the solubilized lipids move directly into the cell, but the bile acid returns to the intestinal lumen. In this formulation, therefore, the rate of absorption would be proportional to the concentration of fatty acid, monoglyceride and cholesterol in each micelle and to the number of micelles present at the aqueous membrane interface. A second possibility is that fatty acid, monoglyceride, and cholesterol uptake from micellar solutions takes place only from the monomer phase of the molecules in equilibrium with the micelle. The rate of absorption from such a system would be proportional to the concentration, of each of the lipolytic products in the monomer phase, and the micelle would serve only as a reservoir for fatty acid, monoglyceride, and cholesterol to maintain this concentration at a maximum value.

Currently available evidence strongly suggests that the latter possibility, outlined diagrammatically in Fig. II-3, is the correct one. Thus, the bile acid micelle merely acts to carry fatty acid, monoglyceride and cholesterol across the unstirred water layer and so effectively overcomes the resistance of this "water" membrane to the free diffusion of individual lipid molecules from the intestinal contents to the microvillus border of the intestinal mucosal cell.

Certain quantitative aspects of this model are of great physiological importance and are shown in diagrammatic fashion in Fig. II-4. Consider first the situation where cell uptake is limiting to the rate of absorption and where there is no unstirred water layer or bile acid micelle present. In this situation the maximum rate of uptake equals the product of the maximum aqueous solubility of a particular lipid times its appropriate passive permeability coefficient. As shown by the solid line in Fig. II-4, this maximum rate of uptake decreases as one goes from more polar compounds, like short chain fatty acids, to less polar compounds, such as long chain fatty acids and cholesterol.

In the presence of an unstirred water layer the rate of uptake is reduced below these theoretical maximum values since the concentration

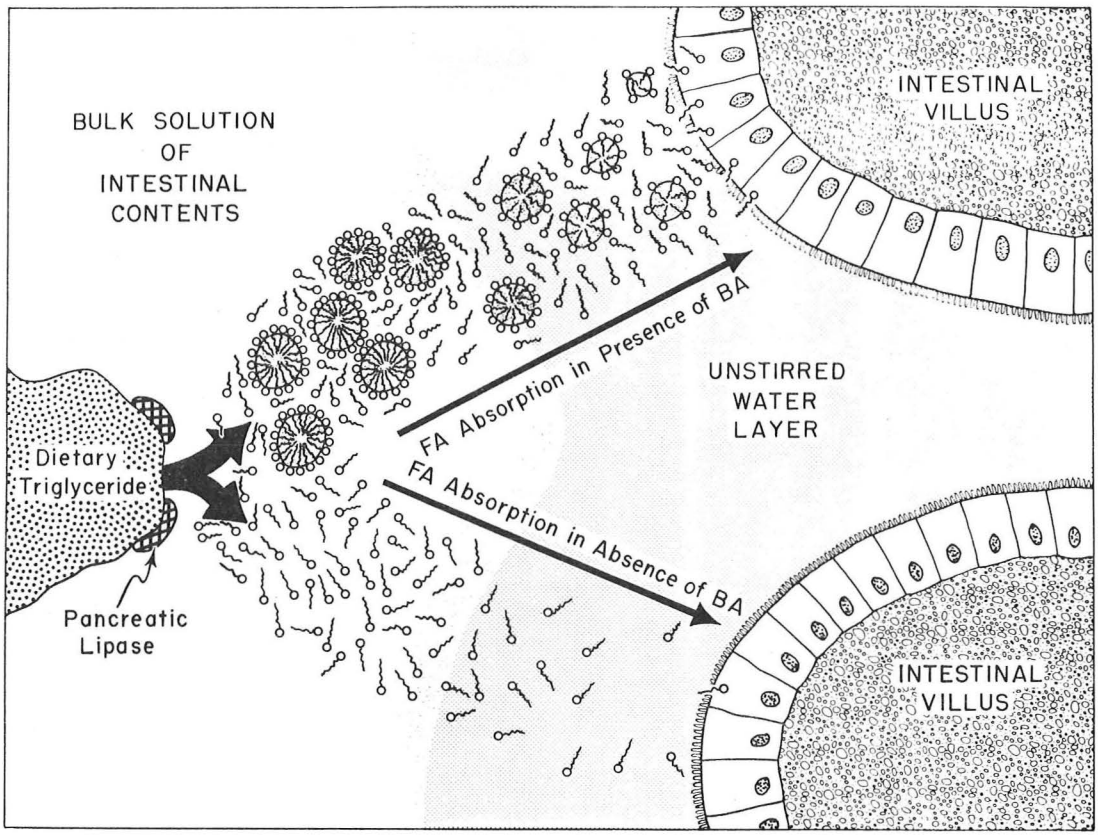

FIG. II-3. Diagrammatic representation of fatty acid absorption into the intestinal mucosal cells in the absence and presence of bile acid micelles. In the absence of bile acid (BA) micelles the individual fatty acid molecules encounter marked resistance in diffusing across the unstirred water layer so that the rate of absorption into the intestinal mucosal cells is relatively slow. In the presence of bile acid micelles, however, this resistance is overcome by diffusion of fatty acid-laden mixed micelles across the unstirred water layer so that the rate of fatty acid absorption is greatly enhanced.

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of the lipid molecules at the aqueous-membrane interface will be less than they are in bulk intestinal contents because of the resistance to diffusion offered by this aqueous diffusion barrier. The magnitude of this effect, however, will be greater for the less polar compound with higher permeability coefficients; hence, in the presence of an unstirred water layer the maximum rate of absorption will be described by the dashed line in Fig. II-4. Thus, the deviation of the dashed line from the solid line is a manifestation of unstirred layer resistance and, as is apparent, this unstirred layer effect is quantitatively unimportant for the polar members of the series but quantitatively very important for the less polar members of the series.

In the presence of bile acid micelles, large amounts of lipid are carried across the unstirred water layer so that the monomer concentration at the

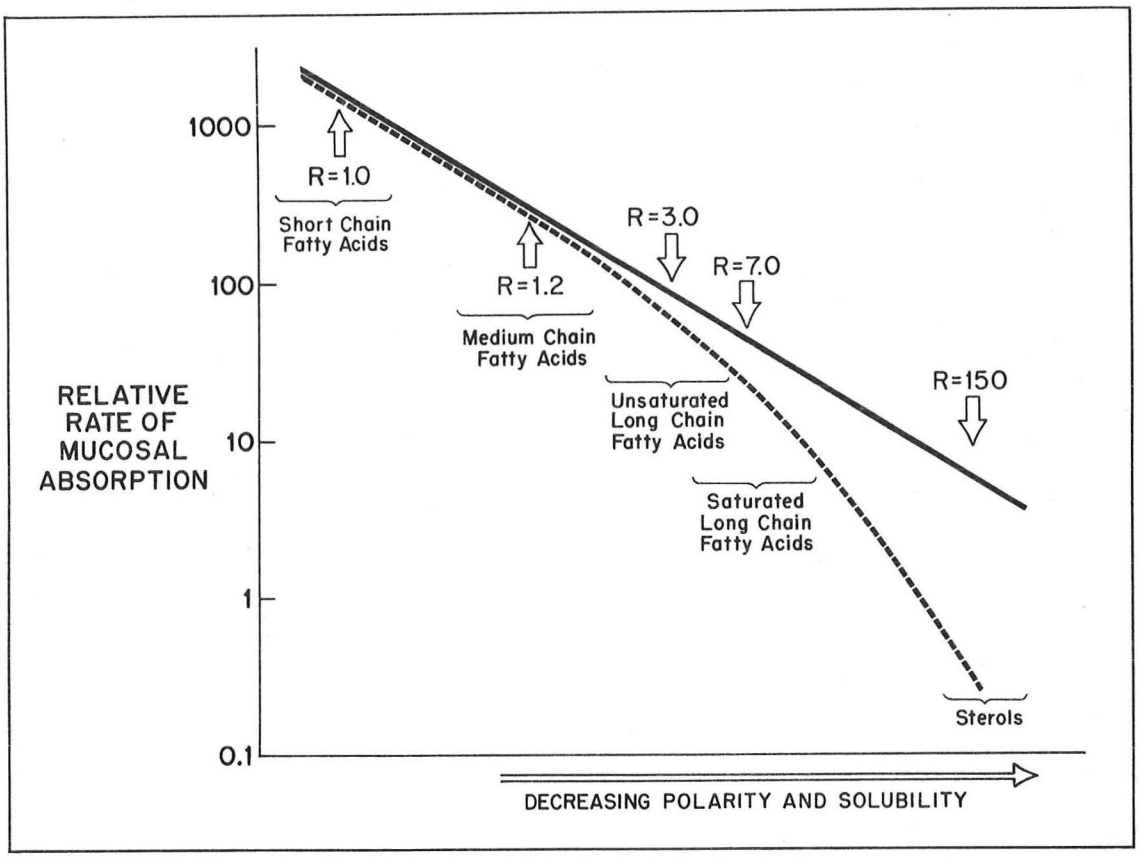

FIG. II-4. The relative rates of mucosal absorption of lipid molecules of different polarity in the presence and absence of bile acid micelles. The solid line shows the relative rate of intestinal mucosal cell uptake for compounds of differing polarity and solubility in the presence of bile acid micelles while the dashed line shows the rates expected in the absence of bile acid. For each group of lipids the ratio R defines the degree to which the presence of bile acid micelles facilitates absorption. This ratio is close to 1 for the short and medium chain-length fatty acids, i.e., bile acid micelles do not significantly enhance mucosal uptake of these compounds. The ratio progressively increases, however, with fatty acids of longer chain length and sterols so that the presence of bile acid micelles significantly enhances the uptake of these particular compounds into the intestinal mucosal cell.

aqueous-membrane interface is maintained at near saturation and the rate of absorption is enhanced. Thus, in the quantitative terms diagramed in Fig. II-4, the function of the bile acid micelle is to overcome unstirred layer resistance, i.e., to move the dashed line upwards toward the solid line. It is apparent that the relative effect of bile acids in facilitating the absorption of various lipids will depend directly upon the relative resistance encountered by a particular group of lipids in crossing the unstirred layer. Thus, the unstirred water layer exerts little resistance to the uptake of short and medium chain length fatty acids: hence, bile acid micelles have essentially no effect in facilitating the mucosal uptake of these compounds.

In contrast, unstirred water layers are essentially rate-limiting for the uptake of longer chain fatty acids and, in particular, for cholesterol so that the presence of bile acid micelles significantly enhances the absorption of these compounds, Stated in another way, in the absence of bile acid micelles in the intestinal lumen short and medium chain fatty acid absorption takes place normally; there is a modest decrease in long chain fatty acid absorption; and there is essentially no cholesterol absorption.

In the intestinal mucosal cells the long chain fatty acids are activated to their CoA derivatives by the enzyme fatty acid:CoA ligase which has a high affinity for long chain fatty acids but which is relatively inactive for medium chain fatty acids. The activated long chain fatty acid thioesters are then esterified to form triglycerides by two pathways: the monoglyceride pathway and the L-α-glycerophosphate pathway, of which the former is quantitatively more important. The enzymes necessary for the synthesis of triglycerides from β-monoglyceride and activated long chain fatty acids are localized in the microsomal fraction. Since the enzymes are purified to the same extent from microsomes they probably exist as an enzyme complex which has been called "triglyceride synthetase". The glycerol backbone for the L-α-glycerophosphate pathway is derived from either glycosis or from monoglyceride lipase. The glycerol is than phosphorylated to form L-α-glycerophosphate. This compound can accept two activated long chain fatty acids to form phosphatidic acid which, in turn, is converted into either phospholipids or triglycerides.

Cholesterol is similarly reesterified in the intestinal mucosal cell by acylation with long chain fatty acids. The enzyme responsible for this reaction, cholesterol esterase, does not require activated fatty acid thioesters and the major amount of enzyme activity is found in the soluble fraction of the mucosal cells.

The resynthesized triglycerides, phospholipids, and cholesterol esters are combined with free cholesterol and a small amount of specific protein in the intestinal mucosal cell to form the final products of fat absorption, chylomicrons and very low density lipoproteins (VLDL). The chemical composition of chylomicrons is approximately 82% triglycerides, 14% phospholipids, 2% cholesterol and cholesterol esters and 2% protein; VLDL have a lower triglyceride and a higher phospholipid content, whereas the cholesterol and protein content is about the same as found in chylomicrons. The specific proteins associated with the two lipoproteins are synthesized in the microsomes, but the exact mechanism by which the proteins associate with the lipids to form the lipoprotein particles remains unclear. However, several lines of evidence indicate that such protein synthesis and incorporation into the lipoprotein particle is essential for the ultimate absorption of fat.

D. Lymphatic and Vascular Phases

The synthesized chylomicrons are relatively large particles approximately 0.5 to 1.0 μm in diameter. The mechanism by which these lipoproteins are transported out of the mucosal cell is still poorly understood: presumbably some type of reverse pinocytosis is operative. Once outside the cell the lipoproteins diffuse through the loose connective tissue of the villus core and enter the central lacteal which has relatively large pores and permits

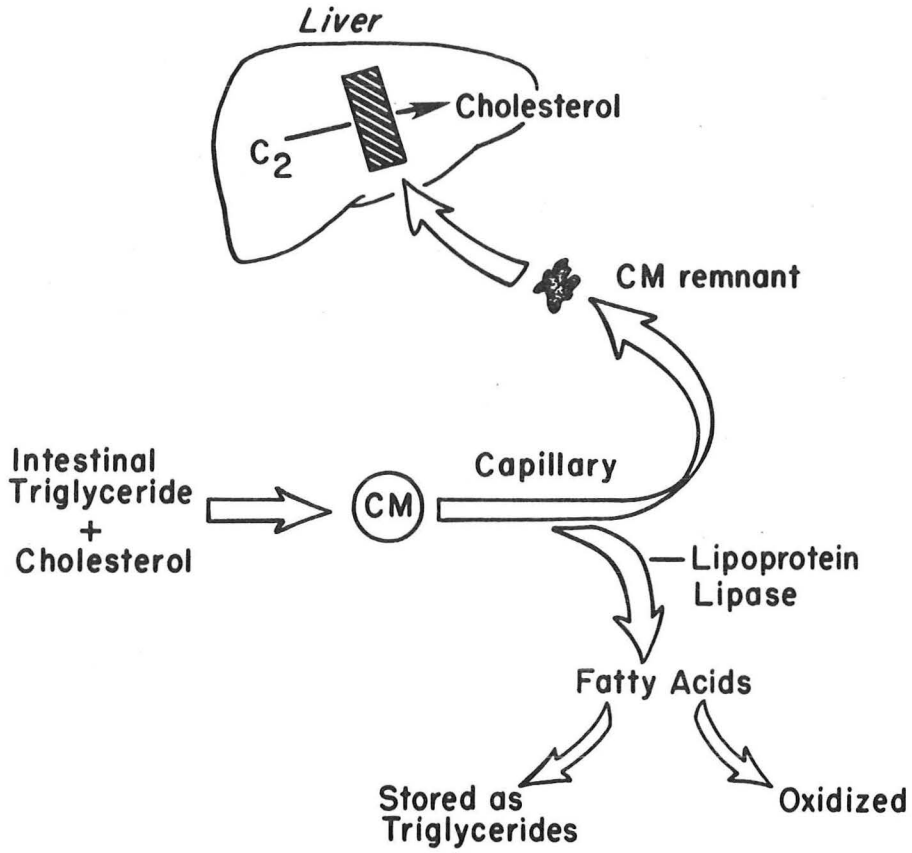

FIG. II-5. Peripheral metabolism of chylomicrons.

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the lipoproteins to enter the vessel. The particles are then transported in the lymphatic system through the intestinal mesentary, up the thoracic duct and, hence, enter the superior vena cava.

As illustrated diagrammatically in Fig. II-5 the dietary lipids ultimately are then delivered to various tissues of the body. As the chylomicrons circulate within the vascular space, they pass through capillary beds in a variety of tissues. Situated in these capillaries is another specific lipase, lipoprotein lipase, which hydrolyzes the long chain fatty acids from all three positions on the triglyceride molecule. These free fatty acids then diffuse from the vascular space into the cytosolic compartment of the cell surrounding the capillary bed. If this process takes place in adipose tissue the free fatty acids are immediately reesterified in the adipocyte and stored as triglyceride. In other tissues such as muscle, the free fatty acids are activated and oxidized as a source of metabolic energy.

With the removal of a significant amount of triglyceride from the chylomicron particle by this mechanism the chylomicron shrinks in size and becomes relatively more rich in protein, phospholipid,cholesterol and cholesterol esters. This triglyceride-depleted particle is referred to as the chylomicron remnant. These remnants, once formed, are essentially quantitatively cleared

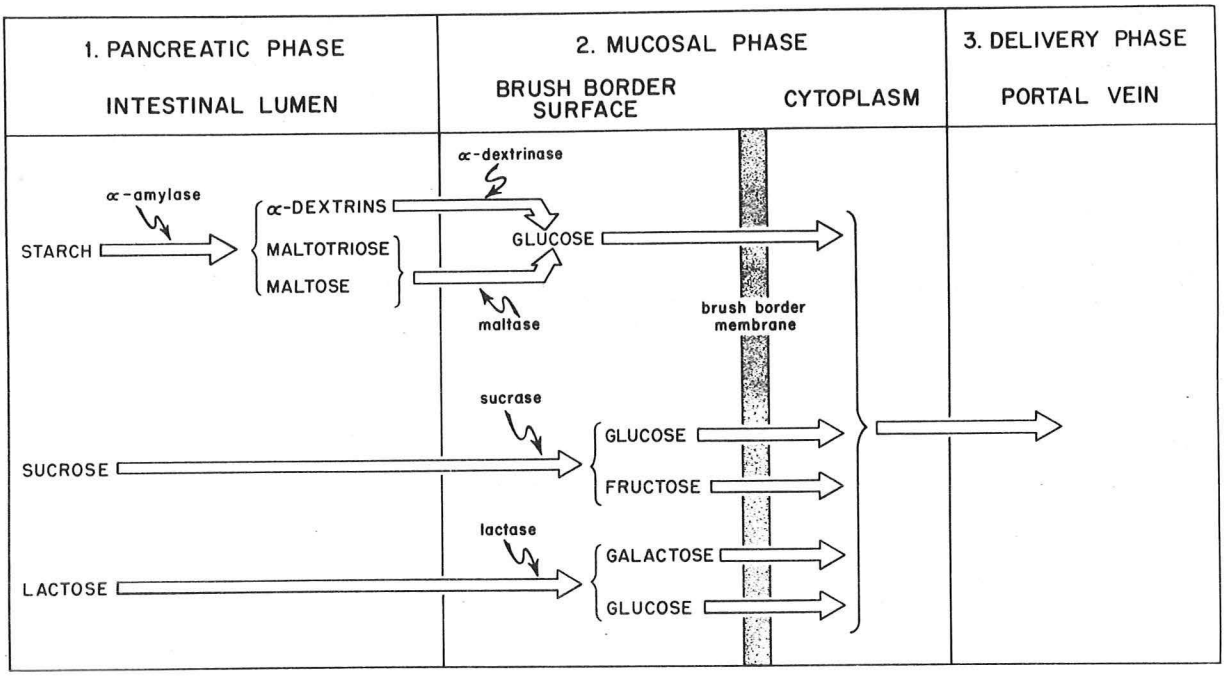

FIG. II-6. Summary of carbohydrate digestion and absorption. Initially, starch is hydrolyzed in the duodenal lumen by pancreatic α-amylase. Further hydrolysis of their initial products and the dietary disaccharides takes place at the brush border membrane through the action of several oligosaccharidases. The final products of the enzymatic processes are transported into the cell through the brush border membrane. Glucose and galactose utilize an active transport system and fructose is transported by facilitated diffusion. Then, the monosaccharides diffuse down their concentration gradient into the portal vein system.

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from the circulation by the liver. Thus, much of the triglyceride of dietary origin is delivered to peripheral tissues through the action of lipoprotein lipase while the majority of the cholesterol of dietary origin is delivered directly to the liver. The uptake of the remnant particle by the liver results in an abrupt increase in the cholesterol content of the liver cell and causes *de novo* cholesterol synthesis from acetyl CoA in the hepatocyte to be inhibited. In this manner the rate of *de novo* cholesterol synthesis by the liver is automatically adjusted to the level of exogenous cholesterol absorbed in the diet from the body.

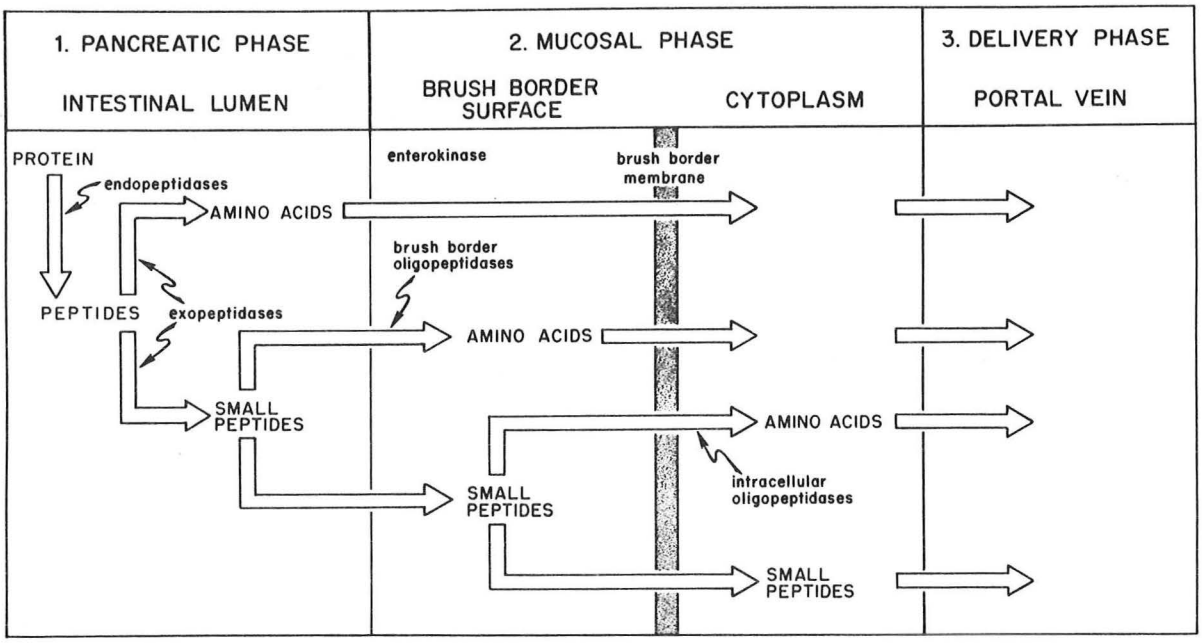

FIG. II-7. Schematic figure representing the different phases of protein digestion and absorption. (1) Endogenous and dietary proteins are hydrolyzed by pancreatic peptidases in the duodenal and jejunal lumen. Note that enterokinase, the activating duodenal enzyme, is located at the brush border surface. Trypsin is liberated through the action of enterokinase on trypsinogen; the liberated trypsin then activates the bulk of the pancreatic propeptidases. The main products released in the pancreatic phase are neutral amino acids and oligopeptides. (2) Brush border oligopeptidases are only able to attack small neutral peptides. Other small peptides cross the brush border membrane and are hydrolyzed by soluble cytoplasmic oligopeptidases. There are several amino acid transport systems in the brush border membrane. (3) The final products of the mucosal phase, amino acids and a small fraction of oligopeptides, diffuse outside the mucosal cells down the concentration gradient to be delivered through the portal vein system.

E. Comparison of Fat Absorption to the Digestion and Absorption of Protein and Carbohydrate

The major steps involved during the intestinal digestion and absorption of complex carbohydrates and proteins are illustrated diagrammatically in Figs. II-6 and II-7. Starches are partially digested by a pancreatic amylase and further digestion of similar saccharides takes place under the influence

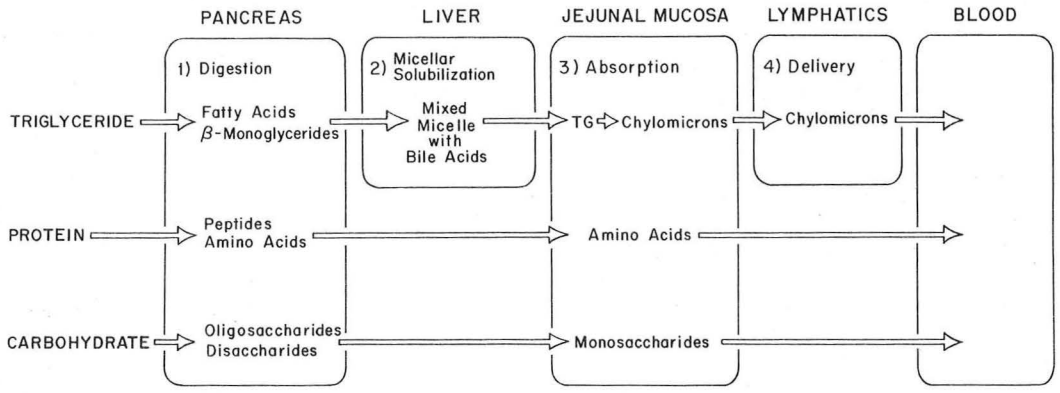

FIG. II-8. A comparison between the four major steps of fat digestion and absorption and the corresponding processes involved in the assimilation of protein and carbohydrate. This diagram emphasizes that the processes of micellar solubilization and delivery of chylomicron through the intestinal lymphatics are not involved in the absorption of these latter two nutrients. Thus, diseases that cause dysfunction at the level of steps 2 and 4 result in the malabsorption only of fat, i.e., isolated steatorrhea, whereas diseases that exert their effect at the level of steps 1 or 3 may produce significant malabsorption of fat, protein, and carbohydrate.

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of enzymes localized on the brush border of the mucosal cell. The resulting monosaccharides are then actively transported across the membrane of the microvilli to the cytosolic compartment and then diffuse into the blood capillary. Similarly, proteins are digested within the intestinal lumen by pancreatic peptidases following which there is further digestion of short chain peptides by enzymes localized on the brush border of the absorptive cell. Free amino acids and short chain peptides are then actively transported into the intestinal mucosal cell and diffuse into the capillary.

As illustrated diagrammatically in Fig. II-8 there are two major differences in the mechanisms of fat versus protein and carbohydrate digestion that have important clinical implications. First, during the digestion of

these three dietary components only the products of the digestion of triglyceride require micellar solubilization. Bile acids are not involved in the solubilization of the digestive products of protein and carbohydrate. Second, there is anatomical separation of the route of absorption of lipids, protein and carbohydrates. All lipid-soluble materials are incorporated into the chylomicron and so pass through the intestinal lymphatic system and enter the circulatory system distal to the liver. In contrast, amino acids and monosaccharides pass directly into the portal circulation and so enter the liver directly. It is evident from these considerations that any disease which affects the pancreas or the jejunal mucosa may result in a diffuse defect in the process of digestion and absorption in which there is malabsorption of all three major caloric sources in the diet, i.e., fat, protein and carbohydrate. In contrast, those diseases which selectively alter the process of micellar solubilization or the lymphatic outflow from the intestine produce a highly selective defect in fat absorption, i.e., selective steatorrhea, but generally do not alter the rates of absorption or protein and carbohydrate.

III. TESTS OF DISORDERED FAT ABSORPTION AND BILE ACID METABOLISM

Numerous tests are usually listed in textbooks to differentiate the various types of malabsorption syndromes. Many of these tests, however, are very nonspecific and of little use. The great majority of the commonly encountered malabsorption syndromes can be differentiated by use of relatively few tests when these tests are properly done and interpreted.

A. Qualitative Stool Fat Determination

In patients who commonly present with a change in the quality or number of bowel movements, the initial differentiation is often between those illnesses that produce simple watery diarrhea and the malabsorption syndromes. The simplest, least expensive test that can be done immediately on such patients is the qualitative stool fat examination. This test may immediately demonstrate that there is an excess amount of lipid in the stool of the affected individual. The actual chemical species present in patients with different types of malabsorption varies from free fatty acids and partial glycerides to undigested triglycerides. Furthermore, the free fatty acids may be present as the fatty acid ion or the protonated fatty acid molecule (depending upon the pH of the stool) and in a dispersed form or in the form of a fatty acid crystal (the saturated fatty acids). In performing the qualitative stool fat examination it is necessary to acidify the stool in order to drive all of the fatty acid ions into the protonated, insoluble form and to warm the specimen in order to melt the saturated fatty acid crystals. Under these conditions, then, all of the lipid species are driven into an insoluble form causing them to phase-out as insoluble oil droplets. If at this time a fat-soluble stain is present in the mixture, then the fat droplets will stain and appear under the microscope as refractile, colored globules. In this test then, a small quantity of stool is mixed on a glass microscope slide with one or two drops of acetic acid and one or two drops of an oil stain such as Sudan III. The mixture is covered with a glass cover slip and briefly warmed. When examined under the hi-dry lens of a microscope usually only one to two small droplets are seen per high-powered field from a specimen obtained from a normal individual. In contrast, many stained oil droplets of varying size are seen in individuals who have significant malabsorption and steatorrhea. A false positive test may be obtained in individuals who have recently ingested a nonabsorbable oil such as mineral oil. Otherwise, this test has the marked advantage of simplicity allowing the physician to make the presumptive diagnosis of steatorrhea immediately after first examining the patient.

B. Quantitative Stool Fat Determination

Quantitative chemical determination of fecal fat is the most reliable measure of identifying 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 output of fat equals approximately 2.9 gm/24 hr. 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

gm/24 hr and 8.7 ± 0.7 gm/24 hr in subjects receiving 100 gm and 200 gm, respectively, of fat in their daily dietary intake. Thus in the individual with normal gastrointestinal function fecal fat is usually <7% of dietary intake; in the face of a typical daily fat intake of 60 to 100 gm this is approximately equivalent to an excretory rate of <6 gm/24 hr. Even under an extreme load of more than 300 gm of fat per day, normal persons absorb >98% of the intake. In the patient with compromised digestive or absorptive capacity, however, the amount of fat in the feces is related to the amount of fat in the diet.

A number of conditions should be met in order to obtain a meaningful measurement of fecal fat output. The patient must be eating a significant amount of fat (60 to 100 gm/day) for several days before as well as during the 72-hour stool collection. Poor intake during the collection 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. This method may lead to incomplete extraction and quantitation of medium chain fatty acids; however, appropriate modifications of this method have yielded accurate results.

The quantitative features of this test are summarized in Fig. III-1 where the level of fecal fat is plotted against the amount of fat eaten in the diet per 24 hours. In the normal individual the intestine has a great reserve capacity for fat absorption so that the fecal fat level will equal only approximately 11 gm/24 hr even when the dietary intake is 300 gm/24 hr. At the other extreme, if the dietary fat intake is reduced to 0 gm/24 hr the fecal fat output equals only 2.9 gm, most of this coming from bacterial lipids and from lipids contained in desquamated intestinal cells. In contrast, in a patient who has just had total small bowel resection, shown by the dotted line, essentially all of the ingested fat will be excreted in the feces. All other forms of malabsorption fall somewhere between these two extremes. The important point to emphasize is that the amount of fat in the feces is a function of how much dietary fat the patient is eating. If that patient is not eating well or is eating a low-fat intake then the presence of mild steatorrhea may be missed. Thus, in performing this test, the patient must be on an adequate fat intake for a sufficiently long period of time that an essentially steady state is achieved during the period of time when 72-hr stool collection is carried out.

C. Quantitative Fecal Nitrogen Determination

Determination of fecal nitrogen provides an indirect measure of protein absorption. The patient should be receiving a balanced protein diet and stool should be collected for at least 72 hours. Depending upon the laboratory, the normal fecal nitrogen excretion equals approximately 2.0 gm/24 hr while on a 80 to 100 gm protein diet. 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

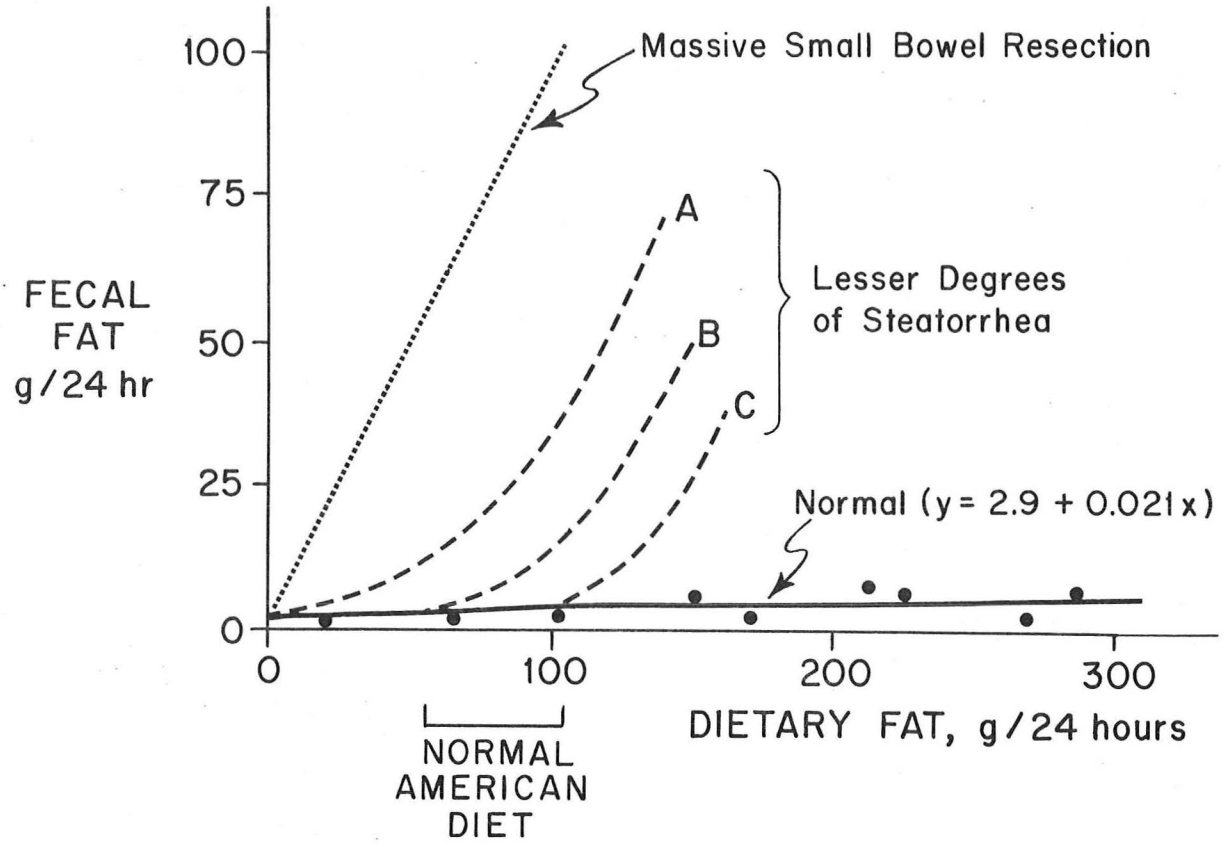


FIG. III-1. Quantitative relationships between the amounts of fat in the diet and the amount excreted in the feces.

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.

D. Xylose Absorption Test

The xylose absorption test commonly is erroneously regarded as a measure of carbohydrate absorption. Xylose, a five-carbon monosaccharide, is absorbed primarily by passive means in the proximal small intestine. This mechanism of absorption is quite different from the carrier-mediated transport

TABLE III-1. MAJOR TESTS USED TO DIFFERENTIATE TYPES OF MALABSORPTION

Test	Test Useful in Evaluation of	Factors Which Cause Artifactually Low Values of the Test	Factors Which Cause Artifactually High Values of the Test
Quantitative fecal fat	Digestive and absorptive capacity for dietary fat	Inadequate fat intake Constipation Incomplete fecal collections	Ingestion of large quantities of castor oil or nut oils
Quantitative fecal nitrogen	Digestion and absorptive capacity for dietary protein	Inadequate protein intake Constipation Incomplete fecal collections	Excessive leakage of plasma proteins into the intestinal lumen (i.e., protein-losing enteropathy)
Xylose absorption test	Functional integrity of the jejunum Presence of massive bacterial overgrowth in the small bowel	Vomiting after administration Delayed gastric emptying Inadequate hydration Intrinsic renal disease Massive ascites Incomplete urine collections Old age	Contamination of urine with feces
Vitamin B_{12} absorption test	Functional integrity of the ileum Presence of massive bacterial overgrowth in the small bowel	Vomiting after administration Inadequate hydration Intrinsic renal disease Incomplete urine collections Presence of subtotal or total gastrectomy	Contamination of urine with feces

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 the malabsorption syndromes.

The test is usually performed by the oral administration of 25 gm of xylose to a fasting patient. 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 and 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 gm 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 subjects over 50 years of age.

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

E. 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 vitamin B_{12}-intrinsic factor complex through the proximal small intestine, binding of the complex to specific sites in the ileum and finally, absorption of vitamin B_{12} into the portal circulation. Depending upon the particular laboratory, excretion of >7%/24 hr of the administered radiolabeled vitamin B_{12} usually is regarded as normal.

There are a number of possible sources of error in the performance of this test. Vomiting after the administration of the radiolabeled vitamin, incomplete urine collection, decreased extracellular volume, and intrinsic renal disease will lead to artifactually low urinary values. In contrast to these errors, contamination of urine with feces containing unabsorbed radiolabeled B_{12} will result in falsely elevated values.

Provided these artifacts are absent, and, in the presence of adequate intrinsic factor, a very low excretory rate, usually <1% to 2%/24 hr, is seen in two situations: 1) in the presence of massive bacterial overgrowth or infestation with certain tape worms in the proximal small intestine, 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.

F. Small Bowel Biopsy

Suction and hydraulic biopsy instruments for procurement of intestinal mucosa have considerably facilitated the diagnosis of malabsorption disorders, particularly those that affect the histologic integrity of the small bowel mucosa. A knowledge of the normal histology present 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 the diagnosis. Table III-2 briefly outlines the major histological findings in those diseases that most typically alter small bowel histology. As is apparent from this table the histological findings in at least five specific disorders affecting the small bowel are unique enough to be essentially diagnostic. These diseases include gluten-enteropathy, Whipple's disease, A-β-lipoproteinemia, amyloidosis and mast cell disease. In addition, nine other diseases are listed where the histological changes evident in the small bowel mucosa are compatible with, but not necessarily diagnostic of, specific diseases. These include radiation enteritis, lymphangiectasia, tropical sprue, nongranulomatous jejunitis, scleroderma, eosinophilic gastroenteritis, dermatitis herpetiformis, hypogammaglobulinemia and infestation with various parasites.

G. Tests of Abnormal Bile Acid Metabolism

Several methods have been described for the separation of bile acids in different biological fluids including column and paper chromatography, thin-layer chromatography and gas-liquid chromatography. Quantification of bile acids has been accomplished principally by methods involving photofluorometry, hydroxy steroid dehydrogenases, or gas-liquid chromatography. In one method bile acids are purified by column and thin-layer chromatography, converted to the trimethysilyl ethers of their methyl esters and quantified by gas-liquid chromatography by hydrogen flame ionization. The use of this procedure in the isolation and quantitation of fecal bile acids allows sterol balance studies to be made in man and laboratory animals without requiring the use of radioisotopes *in vivo*. Extension of this method, however, to the measurement of radiolabeled bile acids in duodenal aspirates has facilitated the study of the kinetics and pool size of bile acids in man.

One problem with a number of methods has been the failure to provide satisfactory resolution of the major conjugated and free bile acids for quantification. Since conjugated bile acids are hydrophilic compounds that are difficult to isolate and directly quantitate from biologic materials, most assays have depended on their conversion to the free bile acids. The use of thin-layer chromatography, however, has eliminated the necessity for prior deconjugation and allows separation and measurement of conjugated bile acids directly. This method has been applied to the study of bile acid levels in serum and small intestinal contents from normal subjects and from patients with disordered bile acid metabolism, such as intrahepatic and extrahepatic cholestasis, massive intestinal resection, and the intestinal stasis syndrome.

Using these various methods, it is now possible to determine the kinetic characteristics of bile acid turnover in intact man by administering a labeled bile acid and serially sampling the bile acid pool by duodenal

TABLE III-2. 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 droplets that stain with fat stains
   - D. *Amyloidosis:* 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:* dilatation 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 liquid-filled macrophages
   - 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 fragmentation of the muscularis mucosa
   - K. *Eosinophilic gastroenteritis:* diffuse infiltration of eosinophils in villi and lamina propria
   - L. *Dermatitis herpetiformis:* varying degrees of villous atrophy 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 submucosal 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.

intubation after cholecystokinin infusion. The semilogarithmic plot of the fall in specific activity of the test bile acid yields a straight line which, when extrapolated to 0 time, provides a measure of the bile acid pool size, while the slope of the line reflects the turnover rate. Using this technique pool size, daily synthesis rates and half-life for individual bile acids have been determined in normal man (Table III-3). Furthermore, when the

TABLE III-3. INDICES OF BILE ACID KINETICS IN NORMAL MAN*

Administered Bile Acid	Half-Life	Daily Synthesis Rate	Exchangeable Pool Size for Administered Bile Acid	Estimated Total Bile Acid Pool Size
	days	*mg/day*	*mg*	*gm*
Glycocholate-^{14}C	1.4 ± 0.2 (3)	533 ± 162 (3)	1,165 ± 403 (4)	
Taurocholate-^{14}C	1.9 ± 0.3 (6)	144 ± 55 (6)	377 ± 130 (6)	
	2.1 (2)	108 (2)	329 (2)	
Cholate-^{14}C		333 ± 149 (10)	1,040 ± 210 (10)	2.3 ± 0.5 (10)
	2.8 ± 1.9 (9)	358 ± 149 (9)	1,180 ± 360 (9)	2.4 ± 0.4 (9)
	2.8 ± 0.9 (8)	360 ± 128 (8)	1,380 ± 532 (8)	3.6 ± 0.9 (7)
	3.0 (2)	195 (2)	865 (2)	
Chenodeoxycholate-^{14}C	5.2 (2)	340 (2)	2,470 (2)	
		162 ± 56 (10)	810 ± 170 (10)	

*± numerals indicate variance, given as 1 SD; numerals in parenthesis indicate number of individual determinations (n).

relative proportions between the main bile acids are known, it is possible to use these data to calculate the size of the total bile acid pool. In normal man this pool has been estimated to equal 2 to 4 gm while the half-life for specific bile acids in the pool varies from 1.4 to 5.2 days (Table III-3). Use of this test in patients with various forms of disordered bile acid metabolism has provided insight into the etiology of the malabsorption seen in certain of these patients. For example, in the ileal dysfunction syndrome the bile acid pool has been shown to be diminished in size and the half-life of specific bile acids greatly shortened.

Recently a new test has been reported that allows differentiation of ileal dysfunction and intestinal stasis syndromes from other forms of malabsorption. A tracer dose of glycine-1-C^{14} cholic acid is administered to the patient and the appearance of radiolabeled carbon dioxide (CO_2) is monitored in the breath. In both of these syndromes there is rapid bacterial deconjugation of the test bile acid with subsequent metabolism of the glycine-1-C^{14} and appearance of labeled CO_2 in the breath. In patients with ileal dysfunction or intestinal stasis, a much higher percentage of the radioactivity appears in breath CO_2 6 hours after the administration of

the dose than in normal individuals or in patients with other forms of steatorrhea. Furthermore, by combining these studies with analysis of the amount of radioactivity in the feces, it is possible to differentiate these two syndromes; the amount of radioactivity appearing in the feces is high in the ileal dysfunction syndrome but is normal in the intestinal stasis syndrome.

IV. SPECIFIC DISEASES RESULTING IN MALABSORPTION OF FAT

The values for the major absorptive studies in diseases that result in malabsorption are presented in Table IV-1. 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. The criteria established for the selection and preparation of these data are listed in the footnotes at the bottom of Table IV-1. 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.

A. Insufficient Intraluminal Pancreatic Enzyme Activity

As shown in Fig. II-1, 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 (Fig. III-8) 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 IV-1 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.

B. Insufficient Intraluminal Bile Acid Activity

The second major step in fat absorption, as illustrated in Fig. II-1, is micellar solubilization of fatty acid and β-monoglyceride and requires adequate intraluminal concentrations of bile acids. In the five disease states listed in category 2, Table IV-1, the primary defect causing malabsorption

TABLE IV-1. REPRESENTATIVE VALUES IN SPECIFIC DISEASES OF THE MAJOR DIAGNOSTIC TESTS USED TO DIFFERENTIATE VARIOUS MALABSORPTION SYNDROMES[a]

Disorder	A. Fecal Fat Excretion[b]		B. Fecal Nitrogen Excretion	C. Urinary Xylose[c] Excretion	D. Urinary Vitamin B_{12} Excretion
	g/24 hr	*% Intake*	*g/24 hr*	*g/5 hr*	*%/24 hr*
Representative normal values	<6	<7	2.0	>4.5	>7.0
1. Insufficient Intraluminal Pancreatic Enzyme Activity					
A. Chronic pancreatitis	37 ± 4.5	34 ± 4.8	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	45 ± 4.7	7.5 ± 1.0		
D. Cystic fibrosis	25 ± 4.1	30	4.2 ± 0.6		
2. Insufficient Intraluminal Bile Acid Activity					
E. Extrahepatic biliary obstruction		30 ± 6.0	1.2 ± 0.2		
F. Intrahepatic disease with jaundice	16 ± 2.0	23 ± 2.0	1.2 ± 0.1	4.3 ± 0.9	12.0 ± 1.0
G. Intrahepatic disease w/o jaundice	19 ± 3.0	19 ± 4.0	1.6 ± 0.3	5.9	
H. Cholecystocolonic fistula	13		1.2		
I. Intestinal stasis syndrome	17 ± 1.9	20 ± 3.5	1.8 ± 0.2	3.0 ± 0.5	0.9 ± 0.3
3. Intramural Small Bowel Disease					
J. Gluten enteropathy	28 ± 1.8	32 ± 4.4	5.0 ± 1.2	2.0 ± 0.3	2.4 ± 1.0
K. Tropical sprue	16 ± 0.6	13 ± 0.8		2.2 ± 0.6	5.1 ± 1.3
L. Skin disease					
1. Dermatitis herpetiformis	9 ± 0.6	8 ± 2.1		3.0 ± 0.6	14.9 ± 1.3
2. Others[d]	8 ± 0.5	8 ± 2.0		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	50 ± 5.9	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 gastroenteritis	14 ± 2.1	17 ± 3.2		2.3 ± 0.7	
Q. Food allergy	19 ± 6.1	52 ± 20	0.7	11.2	
R. Small bowel ischemia					
1. Atherosclerosis	15 ± 1.6	24 ± 0.2		2.0 ± 0.5	6.8
2. Polycythemia vera	20				
3. Vasculitis	14				
4. Köhlmeier-Degos syndrome	26	43		1.9	
S. Small bowel resection					
1. Jejunectomy	9				
2. Massive resection or bypass	49 ± 7.2	49 ± 4.5		2.3 ± 1.2	1.1 ± 0.5
T. Intestinal lymphangiectasia	23 ± 4.0	20 ± 3.0	3.2 ± 1.0	7.8 ± 0.5	
U. A-β-lipoproteinemia		18 ± 2.4		6.2 ± 1.3	19.0 ± 2.6
V. Lymphoma	25 ± 2.8	35 ± 6.9	2.4	2.2 ± 0.5	4.0 ± 0.8
4. Malabsorption Caused by Multiple Defects					
W. Zollinger-Ellison syndrome	24 ± 2.4	26 ± 3.6		3.0 ± 0.8	31
X. Scleroderma	19 ± 2.0	24 ± 3.0	2.1 ± 0.2	2.6 ± 0.4	11.5 ± 2.0
Y. Ileal dysfunction					
1. Ileal resection	24 ± 2.8	25 ± 4.1	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 ± 0.9	18 ± 1.7	2.0 ± 0.2		3.2 ± 0.9
AA. Radiation enteritis	32 ± 15.0	70	6.5 ± 2.3	3.1 ± 0.6	2.7 ± 1.5
5. Malabsorption of Uncertain Etiology					
BB. Mast cell disease	49 ± 21.0	45		4.7 ± 0.3	6.0 ± 3.9
CC. Primary acquired hypogammaglobulinemia	21 ± 3.0	19 ± 2.0	1.2	4.0 ± 1.4	1.9 ± 1.0
DD. Carcinoid syndrome	43 ± 20.0	11		2.4 ± 0.1	
EE. Diabetes mellitis	29 ± 4.2	34 ± 5.0	5.3 ± 0.6	4.0 ± 0.7	10.8
FF. Endocrinopathies					
1. Hyperthyroidism	41 ± 6.1			5.3	
2. Hypoadrenalism	22 ± 3.4	18 ± 1.3			
3. Hypoparathyroidism	33 ± 20.0		2.0	2.5	4.5
4. Pseudohypoparathyroidism	11	35			
GG. Parasitic infestation					
1. Hookworm	11 ± 0.8			1.2 ± 0.1	
2. Strongyloidiasis	26 ± 5.1				
3. Coccidiodomycosis	24 ± 5.9	39 ± 17.0		4.0	
4. Schistosomiasis	10			0.3	
5. Capillariasis	25 ± 6.3			2.7 ± 0.8	
6. Giardiasis	17 ± 2.4	23 ± 4.0	2.4 ± 0.6	2.5 ± 0.3	1.7

[a]All data are expressed as the mean ± 1 SE. In all cases the values of the various tests used were those obtained when the patient was initially seen and the appropriate diagnosis made.

Only cases that had an acceptable quantitation of fecal fat excretion expressed as g per 24 hr or as percentage of fat intake were used in the construction of this table. Where no SE is given the value equals the mean of three or less values.

[b]These values were obtained under a variety of conditions and in the majority the dietary fat intake was not specified.

[c]Data were used only from those cases receiving a 25-g xylose load.

[d]Includes exfoliative dermatitis, erythrodermic psoriasis, eczema.

appears to reside at this step and is the result of diminished effective bile acid activity in the intestinal contents during digestion. In such diseases, one would anticipate isolated steatorrhea, in contrast to the situation in pancreatic insufficiency, with no malabsorption of other major dietary constituents and normal tests of small bowel mucosal integrity. This category of illnesses includes those diseases where there is interference with secretion of bile acids into the intestine or where there is intraluminal destruction of bile acids.

Intra- or extrahepatic biliary obstruction. In the presence of extrahepatic biliary obstruction or intrahepatic disease, with and without jaundice (Table IV-1, E, F, and G), a diminished amount of conjugated bile acid reaches the intestinal lumen. Steatorrhea is mild, varying from 16 to 19 g per 24 hr (from 19 to 30% of intake) and protein excretion is normal (1.2 to 1.6 g per 24 hr). Xylose and B_{12} absorption as well as small bowel morphology is usually normal.

Cholecystocolonic fistula. The cholecystocolonic fistula is the second most common fistula between the gallbladder and gastrointestinal tract and effectively shunts conjugated bile acids away from the small intestine. As shown in Table IV-1 (H) the associated steatorrhea again is mild (13 g per 24 hr) while protein absorption is normal.

Intestinal stasis syndrome. A number of anatomic and motility derangements of the gastrointestinal tract such as multiple strictures, surgical blind loops, afferent loop partial obstruction, enteric strictures with fistulas, multiple jejunal diverticuli, diabetic neuropathy, and scleroderma may give rise to the intestinal stasis or blind loop syndrome. The common feature in this syndrome is massive bacterial proliferation in the proximal small bowel secondary to stasis of intestinal contents. This bacterial overgrowth has a number of important metabolic effects. First, the bacteria are capable of causing significant deconjugation and dehydroxylation of bile acids within the intestinal lumen. The possibilities exist, therefore, that the steatorrhea seen in this syndrome is the result either of a direct toxic effect of unconjugated bile acids on the intestinal mucosa or of a decrease in concentration of conjugated bile acids within the intestinal contents. Current evidence favors the latter possibility. It has been demonstrated, for example, that orally administered, conjugated bile acids decreased steatorrhea in a patient with multiple jejunal diverticulosis and in dogs with experimental blind loops. Furthermore, intestinal mucosal biopsies usually have failed to show abnormalities despite the presence of high concentrations of unconjugated bile acids. Second, the bacteria also are capable of binding the B_{12}-intrinsic factor complex and preventing its absorption, and of metabolizing xylose.

Thus, the characteristic findings in patients with intestinal stasis syndrome, as shown in Table IV-1 (I), are a mild steatorrhea (17 ± 1.9 g per 24 hr or 20 ± 3.5% of intake) and a very low B_{12} absorption test (0.9 ± 0.3% per 24 hr). Protein absorption usually is normal (1.8 ± 0.2 g per 24 hr) while the xylose test may be normal or low. Characteristically, the abnormal values for fecal fat, B_{12} absorption, and xylose absorption return to normal after administration of appropriate antibiotics for several days

to inhibit bacterial growth in the intestine, and this maneuver, therefore, represents the major means for identification of this syndrome in a given patient.

Several generalizations concerning these diseases are warranted. In all of the conditions in group 2 the single defect appears to be absence of sufficient quantities of bile acid in the intestinal contents while the functional integrity of the small bowel is intact. Under these circumstances, the defect in fat absorption is mild so that the mean fecal fat excretory values are in the range of 13 to 19 g per 24 hr. This is in contrast to the severe steatorrhea encountered in pancreatic insufficiency (group 1) and in many of the diseases that affect the small bowel mucosa (group 3). Protein absorption as well as xylose and B_{12} absorption characteristically are normal except in the intestinal stasis syndrome where B_{12} absorption (and occasionally xylose absorption) typically is depressed.

C. Intramural Small Bowel Disease

The third major step in fat absorption, shown in Fig. II-1 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 the 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 IV-1 (J), there is massive malabsorption of both fat (28 ± 1.8 g per 24 hr or $32 \pm 4.4\%$ 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 III-2 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 non-granulomatous 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 jejunitis. Other histological abnormalities peculiar to these entities are summarized in Table III-2. 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 (Table IV -1, K) 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 (Table IV-1, M) -- 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 III-2). 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. Futhermore, 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 IV-1 (N); 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 in B_{12} absorption (12.8 ± 3.7% per 24 hr). As outlined in Table III-2 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 IV-1 (O) 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 (Table III-2).

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 IV-1 (P,Q), 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, polycythemia rubra vera, and progressive arterial occlusive (Köhlmeier-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 IV-1 (R), 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 Köhlmeier-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 essentilly 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 IV-1, S). 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 lymphangiectasia. The basic defect in intestinal lymphangiectasia 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 (Table IV-1, T) there is a 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 droplets 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 ± 0.8 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 there 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.

D. Malabsorption Due to Multiple Defects

The fourth major category of diseases listed in Table IV-1 contains illnesses where evidence suggests that there is dysfunction of more than one of the major steps in fat absorption outlined in Fig. III. In some illnesses defects at multiple levels may act together to produce malabsorption while in others one of the defects may be relatively more important in specific patients. Often, however, the data are insufficient to distinguish precisely the predominant defect causing steatorrhea.

Zollinger-Ellison syndrome. The excess gastric acid production in this syndrome very likely accounts for the malabsorption and could interfere with normal absorptive processes by at least three different mechanisms. (1) There may be irreversible denaturation of pancreatic enzymes in the proximal small intestine. (2) The very low pH values found in the jejunum also could cause precipitation of glycine conjugated bile acids into a microcrystalline phase. (3) There are multiple nonspecific morphological alterations found in the small bowel mucosa. Hence, steatorrhea observed in this syndrome conceivably could be the consequence of defects at the lipolytic, micellar, and mucosal phases of absorption (Fig. II-1). As shown in Table IV-1 (W), the steatorrhea averages 24 ± 2.4 g per 24 hr (26 ± 3.6% of intake) while xylose absorption is only slightly depressed (3.0 ± 0.8 g per 5 hr) and B_{12} absorption is normal (31% per 24 hr).

Scleroderma. The characteristic light microscopy findings scleroderma include atrophy of the muscular layers with increased deposition of elastin and collage in the submucosa, serosa, and between the smooth muscle bundles of the muscularis externa. Small bowel biopsy is usually reveals a normal mucosa except for an increased number of plasma cells within the lamina propria. However, as listed in Table III-2 the finding of collagen deposition around and between the lobules of Brunner's glands in the submucosal is useful in the diagnosis of small bowel involvement

in scleroderma. Electron microscopic examination has confirmed the essentially normal appearance of the mucosa. Present data stongly suggest that at least two different mechanisms may be responsible for the steatorrhea seen in this disease. First, there are a small number of cases that have mild steatorrhea and very low B_{12} absorption rates; these abnormal findings return essentially to normal after the administration of broad spectrun antibiotics. Thus, this group of patients presumably has the intestinal stasis syndrome secondary to ineffective motility in the proximal small bowel. Second, in other cases the malabsorption may be the result of structural alterations in the bowel wall such as fibrosis, muscular atrophy, and obliterative vasculitis. As outlined in Table IV-1, as a group patients with scleroderma generally have only a moderate degree of steatorrhea (19 ± 2.0 g per 24 hr, or 24 ± 3.0% of intake) but near normal protein absorption (2.1 ± 0.2 g per 24 hr). Xylose absorption is depressed (2.6 ± 0.4 g per 5 hr) while the average rate of B_{12} absorption is normal (11.5 ± 2.0% per 24 hr). In those few cases with the intestinal stasis syndrome, however, the B_{12} absorption test typically is very low.

Ileal dysfunction syndrome. As pointed out at the beginning of the review ileal function is necessary for maintenance of the enterohepatic circulation of bile acid and, hence, for maintenance of adequate concentration of bile acid in the proximal small bowel. Ileal resection or ileal involvement in Crohn's disease leads to excessive bile acid loss, lower mean concentrations of bile acid in the intestinal contents during digestion, and hence, less effective absorption of fat in the jejunum. Dietary fat that is not absorbed in the proximal small intestine is lost into the colon because of compromised or absent ileal function. Thus, the degree of malabsorption seen in patients with ileal dysfunction often is more severe than can be accounted for simply by inadequate intraluminal bile acid concentrations and probably is the consequence of the combined effects of interruption of the enterohepatic circulation of bile acid and loss of ileal reserve absorptive capacity. The degree of steatorrhea (Table IV-1, Y) varies greatly in individual patients depending upon the degree of ileal resection or dysfunction. There often is an associated watery diarrhea. Typically xylose absorption is normal, while B_{12} absorption characteristically is very low.

Postgastrectomy. Following gastric resection, particularly with a Billroth II type of anastomosis, steatorrhea arises because of interference with absorptive processes at several steps. The loss of pyloric function with anastomosis of the gastric remnant to the jejunum with bypass of the duodenum leads to a poor secretory response of the pancreas to meals and to poor mixing of food with bile acids and pancreatic enzymes. In addition, rapid intestinal transit may reduce contact time between the intestinal contents and the mucosal absorptive cells. Histological abnormalities including jejunal villus atrophy also have been described in postgastrectomy malabsorption, however, the relative infrequency of this finding and the poor correlation with the degree of steatorrhea makes it unlikely that this histological finding contributes significantly to postgastrectomy malabsorption. Finally, rarely massive bacterial overgrowth may occur in the afferent jejunal loop and gives rise to a true intestinal stasis syndrome. As seen in Table IV-1 (Z), the degree of steatorrhea following gastric resections generally is mild (16 ± 0.9 g per 24 hr or 18 ± 1.7% of intake) although this depends to some degree upon the type of operation. Nitrogen absorption in the reported cases is near normal (2.0 ± 0.2 g per 24 hr). Vitamin B_{12} absorption has been reported to be low in a

number of cases and may arise for at least three reasons: (1) diminished intrinsic factor secretion in the gastric remnant, (2) rapid passage of dietary B_{12} through the gastric remnant preventing adequate binding to intrinsic factor, and (3) the presence of afferent loop bacterial overgrowth with the intestinal stasis syndrome. Correction of B_{12} absorption with intrinsic factor following appropriate antibiotic therapy should help elucidate the particular defect present in specific individuals.

Radiation enteritis. Malabsorption of fat following irradiation most often is associated with therapy for abdominal and pelvic malignancies and probably is the result of production of multiple defects in the physiological process of fat absorption. First, destruction of the intestinal wall by ionizing radiation must play an important role. The histological changes are fairly characteristic and are listed in Table III-2. These alterations are influenced by the dose of radiation and by the time interval following irradiation. Initially, the villi and crypts are shortened and there is a cellular infiltration of the lamina propria with polymorphonuclear leukocytes and plasma cells and submucosal edema. With higher doses of radiation there is superficial ulceration of the mucosa and endarteritis of submucosal vessels with thrombosis, infarction, and deeper ulceration. Connective tissue proliferation occurs intially in the serosal coat; later it extends to the submucosal layer and may be accompanied by submucosal lymphatic obstruction and dilation. Second, with irradiation damage involving the ileum there may be interruption of the enterophepatic circulation of bile acids and development of an ileal dysfunction syndrome. This possibility is suggested by the finding of increased rates of disappearance of sodium taurocholate-24-C^{14} from duodenal samples in a patient with structural alterations of the distal small bowel secondary to irradiation. The degree of steatorrhea varies considerably (Table IV-1 AA), and averages 32 $\pm$ 15.0 g per 24 hr and significant azotorrhea also may be present (6.5 $\pm$ 2.3 g per 24 hr). Both the xylose and B_{12} absorption tests may be markedly depressed depending upon the area of the small intestine primarily receiving irradiation.

E. Malabsorption of Uncertain Etiology

The final category of diseases listed in Table IV-1 include those clinical entities where the pathogenesis of the malabsorption syndrome is poorly understood.

Mast cell disease. Involvement by the mast cell may range from infiltration of the skin, presenting as urticaria pigmentosa, to more extensive accumulation in the organs of the reticuloendoethelial system, which clinically resembles a slowly progressive reticulosis. The production of a number of metabolic products such as histamine, hyaluronic acid, and serotonin has been attributed to the mast cell, and many of the symptoms seen in patients with this disease are suggestive of excessive histamine release. Steatorrhea rarely has been recorded as a manifestation of systemic mast cell disease. It is not known what role the invasion of the intestinal wall by mast cells or the release of histamine or other products may play on the causation of steatorrhea. In one case of mast cell disease with

steatorrhea mast cell invasion of the gastrointestinal tract has been demonstrated (Table III-2). In another patient, mast cells were not a prominent finding in small bowel biopsy specimens that revealed, instead, stunted, clubbed villi and a mucosal and submucosal infiltrate of eosinophils. Increased histamine levels suggest that gastric acid hypersecretion may be responsible for the steatorrhea but gastric acid studies have yielded variable results. It is also possible that histamine or other mast cell products may impair fat absorption by influencing intestinal motility. As shown in Table IV-1 (BB) steatorrhea is relatively severe (49 ± 21.0 g per 24 hr) while the xylose and B_{12} absorption tests have yielded near normal results.

The hypogammaglobulinemias. Of the various types of hypogammaglobulinemias primary acquired hypogammaglobulinemia most frequently has been associated with steatorrhea. Other forms of hypogammaglobulinemia including dysgammaglobulinemi with nodular lymphoid hyperplasia, congenital hypogammaglobulinemia, and type 3 dysgammaglobulinemia more rarely have been reported to be associated with malabsorption. While it is often stated that the malabsorption is a consequence of disturbed equilibrium of the intestinal bacterial flora there are no firm data to establish this etiology. At present, the cause of steatorrhea seen in association with dysgammaglobulinemic states is unknown. As shown in Table IV-1 - (CC) the steatorrhea is mild (21 ± 3.0 g per 24 hr or 19 ± 2.0% of intake) while protein absorption has been reported to be normal (1.2 g per 24 hr). Xylose absorption averaged 4.0 ± 1.4 g per 5 hr while B_{12} absorption was suppressed to 1.9 ± 1.0% per 24 hr.

Carcinoid syndrome. Carcinoid is the most common malignant tumor of the appendix and ileum and may occur at any level of the gastrointestinal tract including the gallbladder and pancreatic ducts. The clinical syndrome is well known and usually arises after the primary tumor has metastasized to the liver; it consists of episodes of flushing of the skin, wheezing, and diarrhea, and an endocardial lesion involving the valves of the right side of the heart. Malabsorption of fat only rarely has been associated with the carcinoid syndrome. Experimentally, hypermotility of the intestine has been produced in both man and experimental animals following the administration of 5-hydroxytryptamine and rapid intestinal transit time has been demonstrated in symptomatic patient with malignant carcinoid. The serotonin antagonist, L-methyl-D-lysergic acid-butanolamide bimaleate, is reported to reduce the degree of steatorrhea. Whether other tumor products have a role in the pathogenesis of steatorrhea awaits further evaluation. Other mechanisms of malabsorption that have been proposed include involvement of the small bowel and its blood supply and lymphatics by tumor masses and ileal dysfunction. The small amount of data in these patients makes it difficult to characterize the malabsorptive process. As seen in Table IV-1 (DD), the degree of steatorrhea is quite variable. Urinary xylose excretion is low. No data are available on fecal nitrogen excretion and vitamin B_{12} absorption in patients with documented quantitative fecal fat determinations.

Diabetes mellitus. A number of reports have been published on fat malabsorption occuring as a complication of diabetes mellitus. The clinical syndrome of diabetic steatorrhea includes a history of poorly controlled, insulin-dependent diabetes that usually precedes steatorrhea by 2 or more years. Bowel movements are frequently nocturnal, watery, foul-smelling, and often contain undigested food particles. Diabetic neuropathy including postural hypotension and an abnormal sweat pattern is seen in a majority of patients. While the pathogenesis of diabetic steatorrhea is not understood several mechanisms have been postulated. (1) Occasionally the histological findings of gluten enteropathy are found in intestinal biopsies from diabetics with steatorrhea. Biopsies from most of these patients, however, are normal, and it is likely that these few cases represent gluten enteropathy occuring in patients with coexisting diabetes. (2) In a few other patients pancreatic insufficiency has been incriminated as the cause of the steatorrhea. However, this etiology again has been excluded in the majority of other well studied cases. (3) Because of the clear association with diabetic neuropathy a disturbance of the autonomic nervous system also has been suggested as a mechanism of the steatorrhea. Consistent with this possibility is the demonstration of lesions in the long dendritic processes in the pre- *and* paravertebral sympathetic ganglia which suggests that intestinal sympathetic innervation is altered in patients with diabetic steatorrhea. Indeed, both hyperactivity with rapid intestinal transit and hypoactivity with delayed intestinal transit have been demonstrated in various patients with this syndrome. How such altered autonomic function in the intestine may produce malabsorption has not been clearly elucidated. (4) Finally, in a few cases it is possible that there is excessive bacterial overgrowth in the proximal small intestine with consequent production of the intestinal stasis syndrome. However, it is also clear that this explanation does not apply to the majority of patients with diabetic steatorrhea. Thus, the mechanisms for this malabsorption syndrome remain unclear. As shown in Table IV-1 (EE), the steatorrhea in this condition may be severe (29 ± 4.2 g per 24 hr or 34 ± 5.0% of intake) and may be associated with significant azotorrhea (5.3 ± 0.6 g per 24 hr). The xylose and B_{12} absorption studies, however, on the average are near abnormal, 4.0 ± 0.7 g per 5 hr and 10.8% per 24 hr, respectively.

Endocrinopathies. Relatively little attention has been directed towards the role of endocrine glands in small intestinal structure and function. Studies in laboratory animals, however, have demonstrated hormonal influence on intestinal absorption, and in humans examples of steatorrhea have been cited in cases with hyperthyroidism, hypoadrenalism, hypoparathyroidism, and pseudohypoparathyroidism. The disappearance of steatorrhea following treatment of the underlying endocrine disorder or its reappearance when therapy is discontinued supports a causal relationship. Steatorrhea rarely has accompanied thyrotoxicosis and has disappeared following antithyroid medication of partial thyroidectomy (Table IV-1, FF). Several patients with Addison's disease also have been found to have steatorrhea that responds to steroid therapy. A few examples of malabsorption and hypoparathyroidism have been reported. Again, specific therapy exerts a beneficial effect upon intestinal function suggesting that the observed malabsorption is indeed due to the hypoparathyroidism and steatorrhea have been recorded but a relationship, if any, has not been documemted.

Parasitic infestation. A casual relationship between intestinal parasitism and malabsorption is well established. In man, a reasonably convincing connection between parasitic infestation and malabsorption has been described in cases of hookworm, strongyloidiasis, coccidiomycosis schistosomiasis, capillariasis, and giardiasis. These cases involve isolation and identification of a particular parasite, abnormal small bowel findings, and clinical and laboratory improvement following specific chemotherapy. Except for the presence of the parasite in some state of development (Table III-2) nonspecific abnormalities with flattening of the villi, disorientation of epithelial cells, and inflammatory cell infiltrates are noted on mucosal biopsy specimens. The data in Table IV-1 (GG) obtained from over 50 well documented cases of intestinal parasitism and steatorrhea are subdivided according to specific parasitic diseases. In general, the mean level of steatorrhea is moderate and roughly similar for each parasitic group. Xylose excretion is usually depressed.

V. GALLSTONE FORMATION AND CHOLELITHIASIS

A. *Composition and Function of Bile*

Bile is a complex secretion of the hepatocyte whose composition is modified by the absorption of water and electrolytes during its temporary storage in the gallbladder. The major constituents of bile are listed in Table V-1. In addition to electrolytes and water, bile contains a variety of other components, the most abundant of which are bile acids, phospholipids, cholesterol, and bilirubin that together comprise approximately 90% of the dry weight of bile.

TABLE V-1.

	Hepatic bile	Gallbladder bile
Specific gravity	1.008 - 1.016	1.008 - 1.059
Bicarbonate	20 - 25 mEq/liter	8 - 12 mEq/liter
Calcium	8 - 11 mg/100 ml	25 - 28 mEq/liter
Chloride	90 - 100 mEq/liter	16 - 119 mEq/liter
Bilirubin	17 - 71 mg/100 ml	50 - 1000 mg/100 ml
Water	97 - 98%	84%
Mucins	1 - 4%	
Bile Acids	1.24 - 1.72 gm/100 ml	2.3 - 7.7gm/100 ml
Cholesterol	86 - 176 mg/100 ml	100 - 900 mg/100 ml
Fatty Acids	101 - 438 mg/100 ml	80 - 1600 mg/100 ml
Lecithins	250 mg/100 ml	350 mg/100 ml

B. *Biliary Solubilization Mechanisms for Cholesterol*

Bile acids and phospholids appear to be largely responsible for the unique cholesterol solubilizing properties of bile. In order to understand how disturbances in the composition of bile may be implicating in the precipitation of cholesterol from bile and the formation of gallstones, we first must review the role of these compounds in maintaining cholesterol in solution. Since plasma lipoproteins do not appear to be secreted in significant amounts in bile, another means of solubilizing cholesterol must be operative. This is accomplished by the biliary secretion of bile acids. The liver synthesizes these compounds from cholesterol, and eventually they reach the intestinal lumen where they play an important role in fat absorption. They are efficietly reabsorbed by the ileum and resecreted into bile. Because of this efficient enterohepatic circulation, only a small amount of new bile acid is synthesized each day to just balance the amount of bile acid lost in the stool.

Since it will become apparent that the interaction between bile acids, phospholipids and cholesterol is mainly responsible for the solubilization of the latter, the relative concentrations of each of

these components in bile is important and is illustrated in Fig V-1.

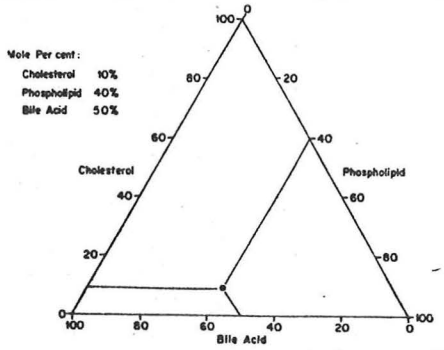


Fig. V-1

Triangular coordinates commonly used to illustrate bile solute composition. A sample, indicated below, is represented by the dot within the triangle.

In this example, bile with a relative molar concentration of 10% cholesterol, 40% phospholipid, and 50% bile acids is indicated by the position of the dot within the triangle. All possible combinations of these three components are thus representable within the area of the triangle.

The molecular interactions between these three compounds are illustrated in Fig V-2. Bile acid molecules contain both a water soluble (hydrophylic)

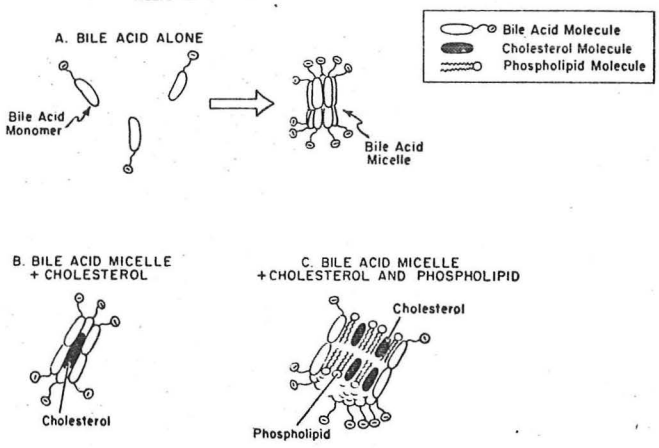


Fig. V-2

Interactions of bile acid, phospholipid, and cholesterol responsible for cholesterol solubilization. A. Aggregation of bile acid monomers in solution to form a bile acid micelle. B. Solubilization of a cholesterol molecule within a bile acid micelle. C. Expansion of the bile acid micelle by phospholipid allowing greater solubilization of cholesterol within each micelle.

and a fat soluble (hydrophobic) portion. Such compounds are termed "amphiphilic" meaning "loving both." At an oil-water interface, these molecules arrange themselves so that their hydrophilic groups lie in the water phase while the hydrophobic groups lie in the oil. At low concentrations in water, bile adid molecules remain in a free form, referred to as a monomer phase, that have no particular associations.

When the concentration of bile acids in the critical micellar concentration, the free monomers aggregate and form a structure called a micelle. This process is ilustrated in Fig V-2. Aggregation occurs by association of their hydrophobic portions, leaving the hydrophilic groups on the surface. The micelle thus represents a tiny droplet of lipid maintained in solution as a result of the surface hydrophilic groups which interact with water. The lipid core of the micelle maintains the important property of being able to act as a solvent for other lipids, thus allowing their solubilization in water.

The ability of a micelle to dissolve other lipids within its core while remaining in aqueous solution is the basic process responsible for the solubilization of cholesterol in bile. When such solubilization occurs, the resulting micelle contains more than one type of lipid and is termed a mixed micelle. Fig V-2 shows a mixed micelle composed of bile acid and cholesterol. Although pure bile acids increase the aqueous solubility of cholesterol, they do so rather poorly and do not appear to incorporate one molecule of cholesterol into each micelle. The properties of such solutions are not capable of adequately explaining the solubilization of levels that are normally present in bile; however, the ability of the micelle to solubilize other lipids does. Phospholipids, such as lecithin, are very soluble in bile acid micelles, and up to two molecules per bile acid molecule can be incorporated into the micelle. This increase in micellar lipid occurs without a loss of aqueous solubility of the micelle, but significantly increases both its molecular weight and size. The expanded micelle is now capable of solubilizing considerably more cholesterol in its lipid core.

If we now return to the three-component diagram, it is possible experimentally to delineate a zone in relation to the concentrations of cholesterol, bile acid, and phospholipid within which cholesterol will be maintained in a single phase, micellar solution. Such a zone is illustrated by the heavily shaded area of Fig V-3. For example, a bile in which cholesterol is maintained in a single phase micellar solution when plotted on these coordinates might be represented by Point A in the diagram.

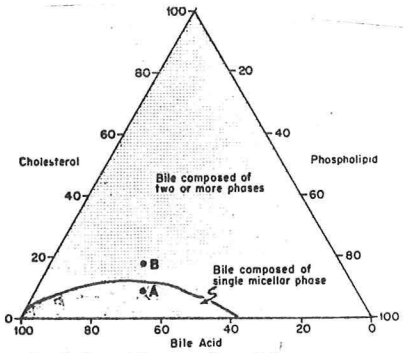


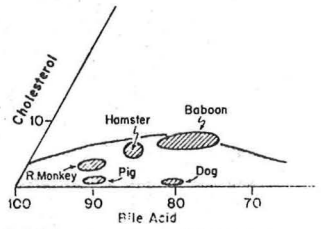
Fig. V-3

In the area outside the micellar zone, cholesterol cannot be maintained in solution (except transiently as an unstable, supersaturated solution) and will precipitate to form a sold crystalline phase in equilibrium with the micellar phase. Point B represents the composition of such a bile. Bile whose composition falls in this area is termed lithogenic and will deposit its excess cholesterol in crystals which may then aggregate to form or enlarge existing gallstones.

C. Gallstone Formation

If these physical and chemical interactions are implicated in the etiology of gallstone formation, some correlation between these parameters and stone formation should be evident. Two types of such correlations exist.

First, the composition of bile from a variety of animal species has been studied and is represented in Fig V-4. For simplicity, only the left lower area of the triangular coordinates are represented.



5. Relative composition of gallbladder bile from several species. Adapted from Redinger and Small.[11]

Fig. V-4

It is apparent from this diagram that the monkey, pig, and dog form bile with a low concentration of cholesterol relative to bile acid and phospholipid. Looked at another way, these animals are capable of solubilizing considerable amounts of cholesterol in addition to that normally present in their bile. These species do not spontaneously form cholesterol gallstones and it is difficult to induce stone formation in them by dietary manipulation. However, in the golden hampster which does not form stones spontaneously, the cholesterol content of bile in this species can be increased by dietary manipulation so that it reaches (saturates) or exceeds (supersaturates) the limits of cholesterol colubility and gallstones form. As also shown in Fig V-4, the baboon normally forms bile that approaches and often exceeds the limits of cholesterol solubility. This species is known to form gallstones spontaneously without dietary manipulation.

Second, there is a similar correlation between the degree of saturation of bile with cholesterol and the incidence of cholesterol gallstones in different ethnic groups of man. In Fig V-5, the estimated prevalence of gallstones in population groups is compared to the mean degree of saturation of their bile with respect to cholesterol. As is evident, the greater the degree of saturation, the higher the prevalence of gallstones in a given population.

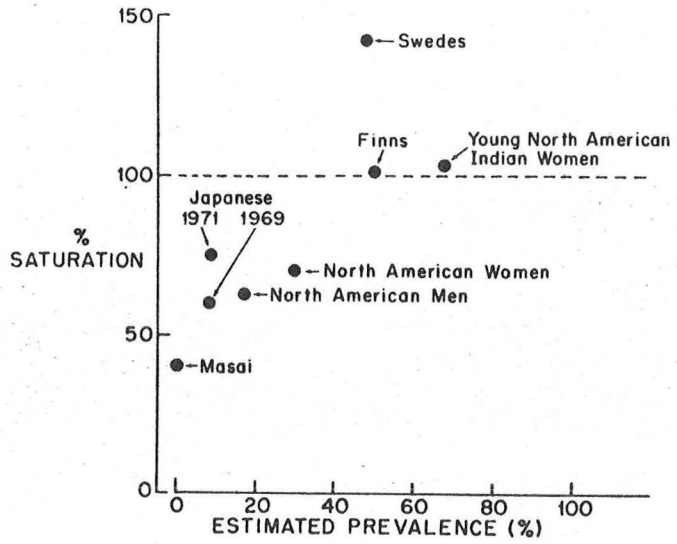


Fig. V-5

Thus, clinical gallbladder disease is unknown in the Masai, an East African nomadic tribe. Based on the study of postmortem bile specimens, members of this tribe appear to secrete a very unsaturated bile with a high ratio of phospholipid and bile acid to cholesterol. Thus, if postmortem specimens reasonably represent the bile composition of this population group, their low incidence of gallstone formation correlates with formation of a relatively unsaturated bile. At the other extreme we find groups having a high incidence of gallstones who, on the average, form a bile that is supersaturated with cholesterol. After an overnight fast, young Chippewa Indian women without gallstones produce bile that is often super saturated with cholesterol. This group has a high incidence of gallstone formation.

In the intermediate zone the correlation is less apparent, but may result from methodological variation between studies. For instance, in Japan, the increase in cholesterol saturation in bile between 1969 and 1971 is probably explainable in this manner: In 1971, in Sweden and Japan, a comparison was made of the composition of bile obtained at surgery for diseases other than those involving the biliary tree. Chemical analyses were performed in the same laboratory, and the degree of saturation correlated with thie apparent incidence of gallstones in these two countries.

If the formation of an abnormal bile is responsible for gallstone formation, one must question whether the liver or the gallbladder is at fault. In 1965 Burnett was the first to report chemical analysis of gallbladder and hepatic bile obtained during biliary tract surgery. He found hepatic bile to have a reduced content of bile acids in about one-half of patients with gallstones while phospholipid levels were only occasionaly lower than normal, and concluded that the liver was responsible for the formation of a potentially lithogenic bile. Subsequently, its actual lithogenicity, based on his calculations, was questioned. In 1970, two groups almost simultaneously published reports confirming that the liver was indeed responsible for the formation of lithogenic bile. In a study of bile composition in a group of predominantly female American Indians undergoing cholecystectomy for gallstones, Small and Rapo found that the hepatic bile was supersaturated while that present in the gallbladder was saturated with respect to cholesterol. These findings are illustrated in Fig V-6.

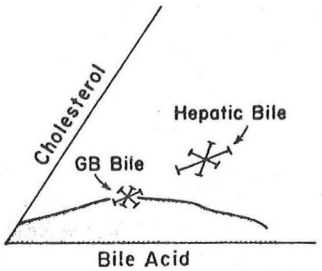


Fig. V-6

At the same time, Vlahcevic et al described a similar abnormality of hepatic bile in a series of men undergoing cholecystectomy for gallstones.

The interpretation of these results was complicated by the unknown effects of fasting, premedication, anesthesia, and surgical stress on bile composition. These studies did, however, include for comparison a small number of patients without gallstones whose hepatic biles were well within the limits of micellar solubilization. Thus, it appears that hepatic bile of patients with cholesterol gallstones has a reduced ability to solubilize cholesterol when compared to bile of patients without gallstones. Also, the small number of patients operated upon for the pigment stones, bile from the pigment stones, bile from both the common duct and gallbladder was again well within the limits of cholesterol solubilization. These results indicate that the presence of gallstones per se does not appear to induce production of a lithogenic bile. Furthermore, samples of bile may be obtained without a laparotomy by placing a tube in the duodenum and aspirating specimens of bile. Gallbladder bile may be obtained by stimulating gallbladder contraction following intravenous injection of cholescystokinin. Such a technique was used to demonstrate that fasting gallbladder bile of young Chippewa Indian women is more saturated than that of Indian men or Caucasians. These subjects did not have gallstones, and the results therefore indicate that the high-risk Indian females (with respect to gallstone formation) secrete an abnormal bile before stone formation occurs.

Since production of bile that is either saturated or supersaturated with cholesterol appears to set the stage for cholesterol gallstone formation, can we further delineate the cause or causes responsible for this abnormality? Based upon three-component system described earlier, an increase in biliary cholesterol, a decrease in phospholipid or bile acid secretion, or some combination of such alterations may be involved. Unfortunately, balance studies in which bile is continuously sampled while the subject maintains a normal or experimentally varied diet and routine for some time are not techinically possible at the present time. Thus, conclusions will have to be based on the results of intermittent sampling of bile under certain specified conditions. Such data cannot be generalized beyond the immediate situation under which the bile was obtained, since composition may vary in response to a number of unknown factors that are normally operative. However, based on such studies, several facts have already been recognized.

The total amount of bile acids in the body, referred to as the bile acid pool, appears to be significantly reduced in patients with gallstones. The size of this pool can be measured in man using radiolabeled bile acids. On the basis of such investigations, men with gallstones were found to have a total bile acid pool approximately one-half the size of control patients without gallstones. A similar reduction in bile acid pool size in the highrisk Southwest American Indian females with gallstones also was found. A small number of patients in this latter study did not have gallstones but produced lithogenic bile and were found to have a reduced bile acid pool similar to the patients with stones. In another study involving Indian males of the Southwest, a small bile acid pool was found to occur in those patients who secreted a lithogenic bile, whether or not they had demonstrable gallstones. Thus, the presently available data suggest that a reduction in the bile acid pool size precedes cholesterol gallstone formation and may therefore be implicated in the formation of lithogenic bile.

Currently, the metabolic reasons for the small bile acid pool in these patients are not clear. Normally the liver would "sense" the reduced pool size and increase the sunthesis of new bile acids until the pool was returned to normal size. This does not seem to occur in patients with lithogenic bile, and implies that the metabolic defect is in the liver cell.

This reduction in bile acid pool size may be directly responsible for the formation of lithogenic bile or may represent one manifestation of a more basic abnormality responsible for gallstone formation. It does not appear to reflect a special situation limited to the American Indian, since a similiar reduction in pool size was also described in Caucasian males with gallstones. The hypothesis that a reduction in bile acid pool size is the direct cause of stone formation is, however, appealing since an increased incidence of gallstones also has been reported in patients with inflammatory disease and/or resection of the terminal ileum which is the major site of bile acid reabsorption. Loss of this area of bowel results in a reduction of pool size because of the considerable loss of bile acids into the stool.

The exact characterization of the pattern of variation in biliary lipid content is currently of considerable concern since it has recently become apparent that secretion of a saturated or supersaturated bile may be an intermittent phenomenon. Indeed, it has now also been reported that lithogenic bile may occur intermittently even in normal patients. Young asymptomatic Caucasian women, presumably without gallstones, generally will secrete a supersaturated hepatic bile following a 10-12 overnight fast. However, although supersaturated with cholesterol, their bile was less so than comparable studied high-risk Southwest American Indian subjects both with and without gallstones.

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