



Review

Anatomical and physiological parameters affecting gastrointestinal absorption in humans and rats

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Accepted 15 September 2000

Abstract

Anatomical and physiological parameters of the gastrointestinal (GI) tract dramatically affect the rate and extent of absorption of ingested compounds. These parameters must be considered by nutritionists, pharmacologists and toxicologists when describing or modeling absorption. Likewise, interspecies extrapolation (e.g. from rat to human) requires species-to-species comparison of these parameters. The present paper (1) describes the alimentary canal and the barrier to absorption; (2) relates the major sites of absorption; (3) compares the dimensions and surface areas of human and rat intestinal tracts; (4) discusses motility of the gut and transit times through regions of the alimentary canal; (5) explains how luminal contents are altered by physical, chemical and metabolic processes; and (6) describes the flow of blood and lymph from the GI tract to the systemic circulation, including the enterohepatic circulation. Despite strong morphological similarities between humans and rats at the microscopic level, gross anatomical differences in the relative absorptive surface areas provide a basis for concluding that the human GI tract is capable of absorbing materials faster and to a greater extent than that of the rat. Differences in the environment of the GI lumen of the two species make it possible to infer which substances are more likely to be present in a dissolved/non-ionized state for each species. Taken together, these differences may be of sufficient magnitude to alter the assessment of risks/benefits for a given compound when those risks/benefits are based on interspecies extrapolations. © 2001 Elsevier Science Ltd. All rights reserved.

Keywords: Gastrointestinal tract; Alimentary canal; Enteric; Oral; Absorption; Anatomy; Physiology; Morphology

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Abbreviations: GI, gastrointestinal

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1. Introduction

Scientists from many disciplines need to understand how orally administered compounds enter the body. Nutritionists want to know how nutrients are extracted from food and absorbed so they may be used by the body. Pharmacologists design drug formulations to optimize absorption and thereby blood levels of a pharmaceutical. Toxicologists are interested in the extent to which xenobiotics enter the body and become available to (adversely) affect it. Information about absorption is necessary to model and predict the kinetics of a compound within a given species or to extrapolate between species (e.g. from rats to humans). Physiologically-based pharmacokinetic models and biologically motivated models are valuable tools for such modeling, predicting and extrapolating, but they require quantitative, as well as qualitative, knowledge about the biological systems under study.

Many factors influence a chemical's rate and extent of absorption after oral intake (Aungst and Shen, 1986; Rozman and Klaassen, 1996). These may be readily categorized into factors that are inherent either to the agent or to the absorptive interface of the animal species under study. Physicochemical properties of a compound are perhaps most important; these include the lipophilicity, ionization state and molecular size of a chemical. These properties are independent of the test species. Absorption also can be greatly affected by other materials present in the gastrointestinal (GI) tract; those other materials can be the vehicle (solvent) used in a laboratory experiment or the food eaten prior to or concomitantly with the ingestion of the chemical. While these factors depend upon the diet of the test species, they are largely physical and chemical factors that are readily modeled. Perhaps the most enigmatic properties that affect absorption, and the ones that cause the greatest interspecies differences, are those that are specific to the test organism: the anatomy and physiology of the GI tract.

The GI tract of humans has many morphological similarities with those of most test species, especially at the level of microscopic observation (Iatropoulos, 1986). The body of research that has revealed how lipids cross the intestinal epithelium, how proteins and carbohydrates are processed, and many of the details regarding the activity of intestinal hormones and digestive enzymes in humans was generated using animal models. Despite these strong interspecies similarities, there are significant differences among species with regard to the amounts and locations of absorptive epithelia, as well as the nature of luminal contents. These differences are likely to play an important role in the degree to which drugs or toxicants are absorbed and in the rate of uptake of such substances. Both are important to consider when describing pharmac/toxicokinetics or when developing physiologically-based pharmacokinetic models.

Although the specific features of the GI tract may be critical determinants of absorption, their significance is often overlooked. This paper provides an overview of the digestion and absorption processes occurring within the alimentary canal and focuses on those anatomical and physiological features that are important to absorption of nutrients and non-nutrients in humans and rats.

2. General description of the alimentary canal

The alimentary canal (Fig. 1) is essentially an open-ended, epithelium-lined tube that extends from the mouth to the anus. Entry into the body proper requires traversing the epithelium and eventually entering the systemic circulation. When viewed in such a manner, it becomes clear that the lumen and its contents are considered to be outside the body proper: the lumen can be conceptualized as a tunnel of the environment through the body, and the wall of the alimentary canal as the interface between the environment and the circulatory system (Granger et al., 1985; Vander et al., 1985). The main functions of the alimentary canal are the digestion of food, the absorption of nutrients, and the propulsion of material through the digestive tract.

The mouth is the entry to the alimentary canal and the site at which the digestive process begins. Ingested material is physically broken down and mixed with saliva by chewing (mastication). In addition to carrying enzymes that initiate the breakdown of carbohydrates and fats, saliva also lubricates the ingested material to aid in swallowing (deglutition).

The pharynx and esophagus are hollow, muscular structures that serve as tandem conduits for the transfer of ingested material from the mouth to the stomach. In humans, the pharynx, a common passageway for the respiratory and digestive systems, is continuous anteriorly with the mouth and nasal cavity and inferiorly with the esophagus and larynx. (As used herein, *pharynx* refers only to the combined oral and laryngeal regions because, under normal conditions, the nasopharynx does not participate in ingestion or swallowing.) In the rat, the pharynx is divided into a respiratory region (an elongated nasopharynx) and a digestive region (analogous to the human's laryngopharynx). There is no oropharynx in the rat because the epiglottis rests against the palate and separates the nasal cavity from the oral cavity. A comparison of the oral and upper respiratory regions of rats and humans has been published elsewhere (DeSesso, 1993).

Within the stomach, muscular contractions mix masticated food with secreted enzymes to form chyme, a semifluid mixture of solutes, emulsion particles and suspended material. Chyme is then released from the stomach to the small intestine via the pylorus, a muscular

ring that separates the two. Both humans and rats have a single-chambered stomach, but the stomach of the rat, like that of all rodents, exhibits two distinctly different, grossly discernible regions. The forestomach, which is lined by stratified epithelium, is an entry from the esophagus and a site of bacterial digestion, while the glandular stomach possesses a secretory epithelium responsible for releasing acidic secretions and proenzymes (Fig. 2A). The anatomical landmark that separates these two regions is the limiting ridge, which is a three-dimensional structure that closes the orifice to the esophagus during retching and thus prevents rodents from vomiting. In contrast, the human stomach is entirely secretory in nature (Fig. 2B).

The small intestine is the major site for digestion and the absorption of nutrients, water and electrolytes. It is divided along its length into three unequally sized portions: the duodenum, the jejunum and the ileum. Most absorption occurs in the duodenum and the proximal half of the jejunum; the major mechanisms of absorption are passive diffusion, facilitated diffusion, active transport, pinocytosis (especially in neonates), and solvent drag or convection (as water moves through membrane pores in response to an osmotic gradient, small solutes pass through, too) (Chhabra and Eastin, 1984; Hoensch and Schwenk, 1984; Granger et al., 1985; Pappenheimer

and Reiss, 1987; Kararli, 1989; Pappenheimer, 1990; Guyton and Hall, 1996).

The absorption of water and electrolytes also occurs in the large intestine. Substances that escaped from the ileum but have properties favorable for absorption and substances formed by bacterial metabolism are absorbed as well. In fact, most nutrient processing in the large intestine is due to bacteria; little processing occurs as the result of intestinal mucosal/secretory activity. In humans, the large intestine is divided into the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, rectum, and anal canal; rats have similar divisions, except that, due to the absence of a true pelvis, they do not have a region designated the sigmoid colon.

3. The nature of the barrier to absorption

From the mouth to the anus, the alimentary canal is lined with a mucous membrane, or mucosa, that serves as the first barrier to entry of materials into the body. The mucosa is composed of an epithelial sheet overlying a thin layer of loose connective tissue (lamina propria) that contains both blood and lymphatic capillaries. Absorption of a substance from the lumen of the

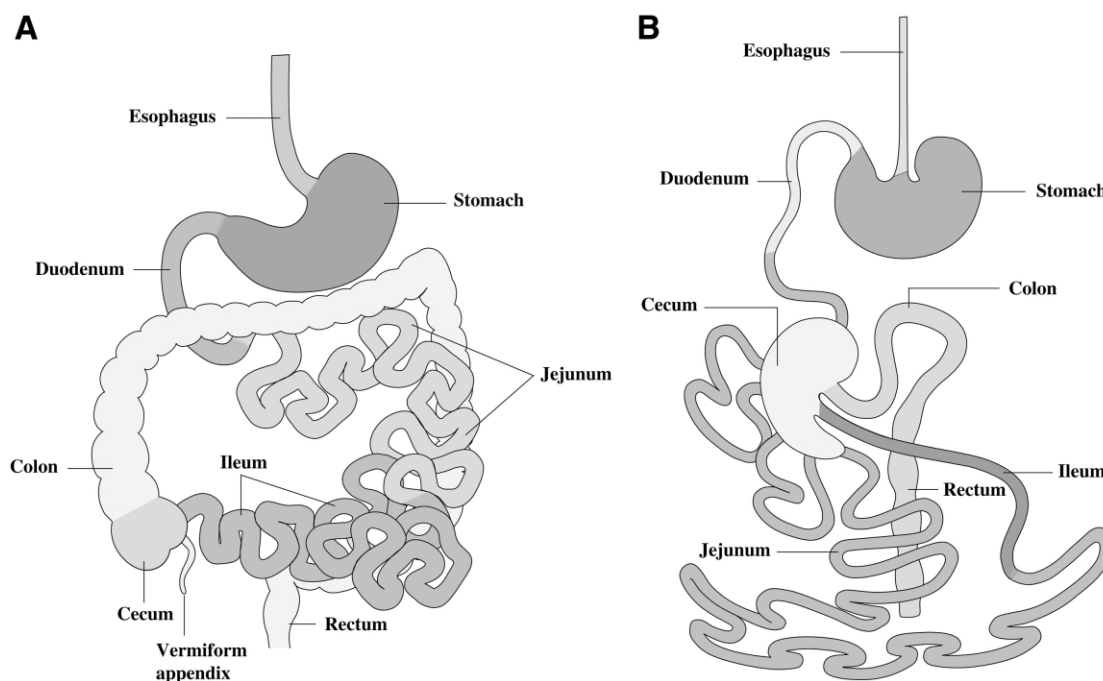


Fig. 1. Overview of the alimentary canals of humans and rats. In the human (A), note the eccentric position for the entry of the esophagus into the stomach. The portal into the small intestine is nearly horizontal. The small intestine is divided into duodenum (the short initial segment), jejunum and ileum, which empties into the large intestine. Note that the diameter of the large intestine decreases as material traverses caudally. The rat's gastrointestinal tract (B) shares the same overall organization as the human's, but with a few important differences. Note that the esophagus enters the stomach at a central location and that the entry into the duodenum faces cranially. The relative lengths of the small intestine differ from the human in that the jejunum makes up nearly the entire small intestine. The cecum of the rat is extremely large and lacks the presence of a vermiform appendix. Note that figures are not drawn to scale.

alimentary canal usually requires that the substance pass through the epithelium, a portion of the lamina propria, and the walls of the blood or lymph capillaries. Under certain normal conditions, substances can pass through the junctions between epithelial cells (see Pappenheimer and Reiss, 1987; Kararli, 1989; Pappenheimer, 1990).

This can be exacerbated in some disease states, for example cholera (Fasano et al., 1991).

The alimentary canal can be subdivided by function into those regions that serve primarily as conduits to propel ingested substances through the canal (mouth, pharynx, esophagus, lower rectum and anal canal) and

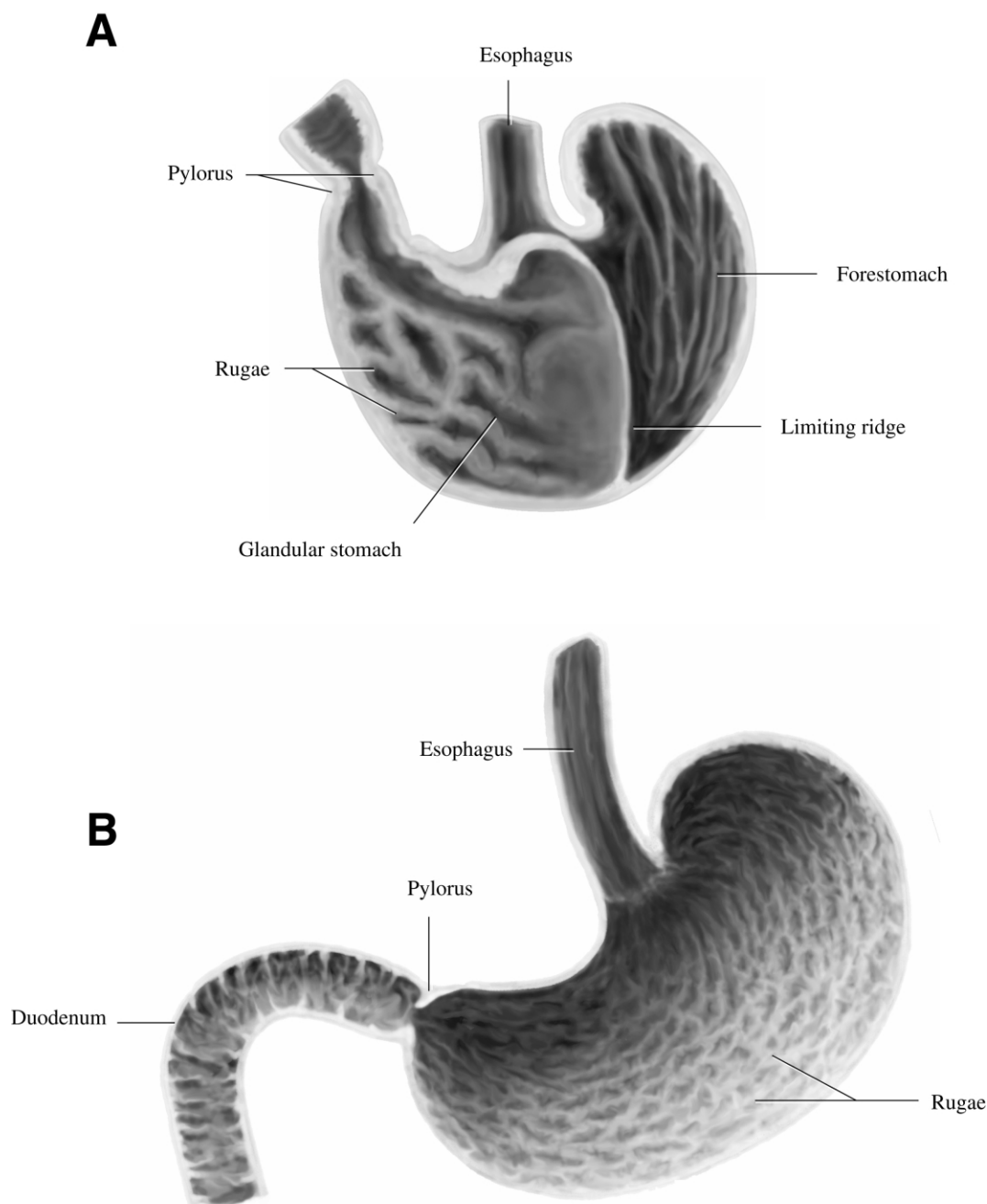


Fig. 2. Comparison of the interior structures of rat and human stomachs. The interior of the rat stomach (A) exhibits two distinctive regions separated by a prominent limiting ridge, which precludes the rat from vomiting. Food entering the stomach is deposited into the forestomach, a non-secretory region with a hardy epithelium. The portion of the stomach that is associated with the exit to the duodenum is the glandular stomach, which is characterized by a delicate secretory epithelium and prominent folds (rugae) that are noticeable when the stomach is empty. Entry of food into the duodenum is regulated by a prominent muscular sphincter, the pylorus. The interior of the human stomach (B) differs from that of the rat in that the entire organ is secretory and there is no forestomach or limiting ridge. The human stomach has numerous rugae.

those that function primarily to digest and absorb the substances (stomach, small intestine, and all but the distal large intestine). The mucosa of the conduit portions of the alimentary canal generally exhibits a moist stratified squamous epithelium (five to seven layers of cells) and a lamina propria that is not richly vascularized. In some regions of the mouth, this epithelium is keratinized, as are epithelia in other body areas subjected to physical stress. The topography of these conduit regions is generally flat with few of the surface irregularities that increase the mucosal surface area. Owing to the multiple layers of epithelial cells and the relatively sparse vascularization of the lamina propria, this type of mucosa is not well adapted to the ready transfer of substances from the lumen to the vascular system.

In contrast, the mucosa of the absorbing portions of the alimentary canal consists of a simple columnar epithelium (i.e. a single cell layer) with a prominent and richly vascularized lamina propria. The mucosa in the absorbing regions of the alimentary canal exhibits a variety of modifications that increase the surface area including folds (plicae), depressions (crypts) and finger-like projections (villi). This increased surface area of the mucosa is conducive to the transfer of substances from the lumen to the vascular system. [The mucosa of the esophagus forms longitudinal folds, and the wall of the stomach has ridges (rugae); these surface modifications allow expansion during swallowing and after a meal, respectively. In addition, some stomach epithelial cells contain microvilli; however, these are secretory in

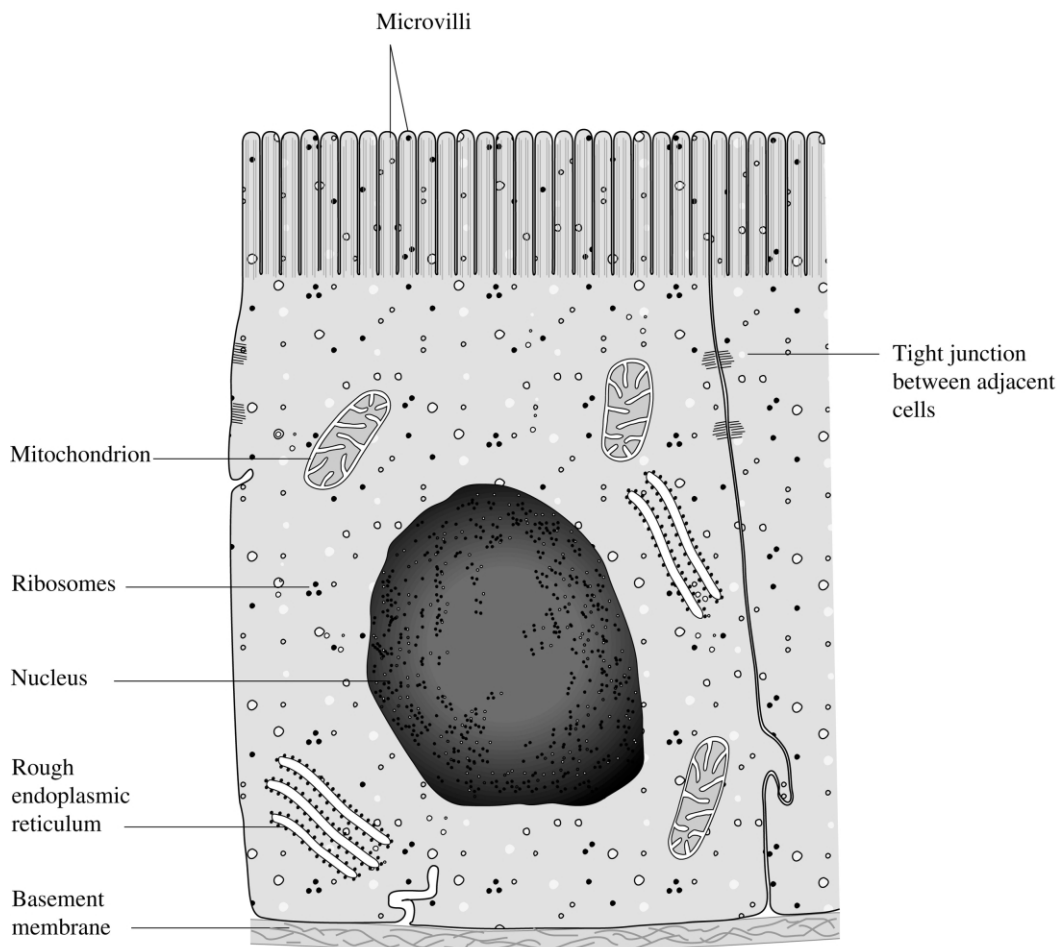


Fig. 3. Diagram of a typical intestinal epithelial cell (enterocyte). Enterocytes are high cuboidal to low columnar epithelial cells that rest on a basement membrane. The cells are joined tightly to neighboring cells by tight junctions. The nucleus resides in the basal portion of the cell. The apical surface of cell exhibits numerous microscopic projections (microvilli) that give the appearance of a “brush border” when seen with a light microscope and that greatly increase the absorptive surface area of the enterocyte. Most substances absorbed from the intestinal lumen must traverse the cytoplasm of an enterocyte. Lipids and fats are absorbed at the base of microvilli and exit the enterocyte at the sides of the cell, beneath the tight junctions; amino acids, triglycerides and carbohydrates traverse the entire cell and exit at the base. Under certain conditions, solvent drag (or convection) can also occur as a paracellular route utilizing partial separation of the tight junctions between intestinal cells to allow the passage of large amounts of water and small solutes.

Table 1
Lengths in centimeters of regions of the human intestinal tract, as reported by various sources

Region	Snyder et al. (1975)	Granger et al. (1985)	Langley et al. (1974)	Van De Graaf (1998)	Vander et al. (1985)	Shepard (1971)	Weiss (1988)	Rozman and Hänninen (1986)	Jacob and Francone (1970)	Magee and Dalley (1986)
Duodenum	21 ^a , 25 ^b , 25–30 ^c	20–30	30	25	20	22				
Jejunum	105 ^a , 190 ^b , 260 ^c	250	150–175	100						
Ileum	156 ^a , 285 ^b , 395 ^c	350	250–270	200						
Total small intestine	282 ^a , 500 ^b , 680 ^c	300 ^b , 600–700 ^c	450		275	300	400	700	550	
Cecum	7 ^{b,c}									
Ascending colon	18 ^{b,c}									
Transverse colon	50 ^{b,c}									
Descending colon	25 ^c , 30 ^b									
Sigmoid colon	40 ^{b,c}									
Rectum	15 ^{b,c}		10–15	20						
Anal canal			5–7.5	2–3 cm of rectum						
Total large intestine	110 ^a , 160 ^{b,c}	125 ^b			120	110	150	150		150–180

^a Physiological length.

^b In vivo length.

^c Anatomical length.

function. It should be noted, however, that the modifications in the esophagus or stomach do not serve to increase absorptive surface area.]

Although the epithelia of the absorbing regions of the alimentary canal are not composed of a uniform population of cells, there is one cell type that is important in the absorption of materials from the lumen and is the predominant cell in all absorbing regions. This cell type is referred to as an enterocyte (Fig. 3). Enterocytes are columnar epithelial cells that are bound to their neighboring cells at the luminal surface by terminal bars (tight junctions). Their apical cell membranes possess numerous microvilli (estimated at 3000–7000 per cell in the small intestine; fewer in the large intestine) which serve to greatly increase the surface area available for absorption (Snyder et al., 1975; Granger et al., 1985). The presence of microvilli on the enterocytes creates the appearance of a brush border that is seen with the light microscope. The absorptive epithelia rest on a basement membrane and possess a carbohydrate-rich glycocalyx coat on the surface of the microvilli.

The lamina propria in the absorptive regions of the alimentary canal possesses a rich supply of blood and lymphatic capillaries. When villi are present, the lymphatic capillaries are slightly dilated, blind-ending tubes that occupy the center of the villus; the blood capillaries form a network of vessels beneath the basement membrane. At various portions of the absorbing regions of the alimentary tract, absorption is favored by mucosal structures such as fenestrations (small holes) in the endothelial cells of the capillaries, or pores of different sizes in the membranes of the enterocytes.

Table 2

Comparison of the anatomical lengths of the intestinal tract and its major subdivisions in humans and rats

Region of intestinal tract	Human ^a		Rat ^b	
	Length (cm)	% of total	Length (cm)	% of total
Duodenum	25	4	9.5–10	8
Jejunum	260	38	90–135	90
Ileum	395	58	2.5–3.5	2
Total small intestine	680	81	125	83
Cecum	7	5	5–7	26
Colon	93	60	9–11	42
Rectum	55 ^c	35	8	32
Total large intestine	155	19	25	17
Total intestinal tract	835		150	

^a Snyder et al. (1975).

^b Hebel and Stromberg (1986).

^c Includes both sigmoid colon and rectum for comparison to the analogous region in the rat.

Underlying the lamina propria is a thin layer of smooth muscle, the muscularis mucosae. The muscularis mucosae is not present in all regions of the alimentary canal, but in regions of active absorption such as the small intestine, it is well developed and even extends up into the central cores of the villi. The function of this muscular layer appears to be related to the rhythmic movements of the villi that agitate the layer of intestinal secretions and chyme that are in contact with the epithelium (the unstirred layer) and thus promote absorption.

4. Sites of absorption

While the systemic absorption of orally ingested materials takes place mainly in the small and large intestines (particularly in the duodenum and proximal jejunum), absorption can and does take place at other sites along the alimentary canal as well. The most important non-intestinal site of absorption is the stomach, which is capable of absorbing non-ionized, lipophilic molecules of moderate size. However, absorption there is limited by the relatively small epithelial surface area

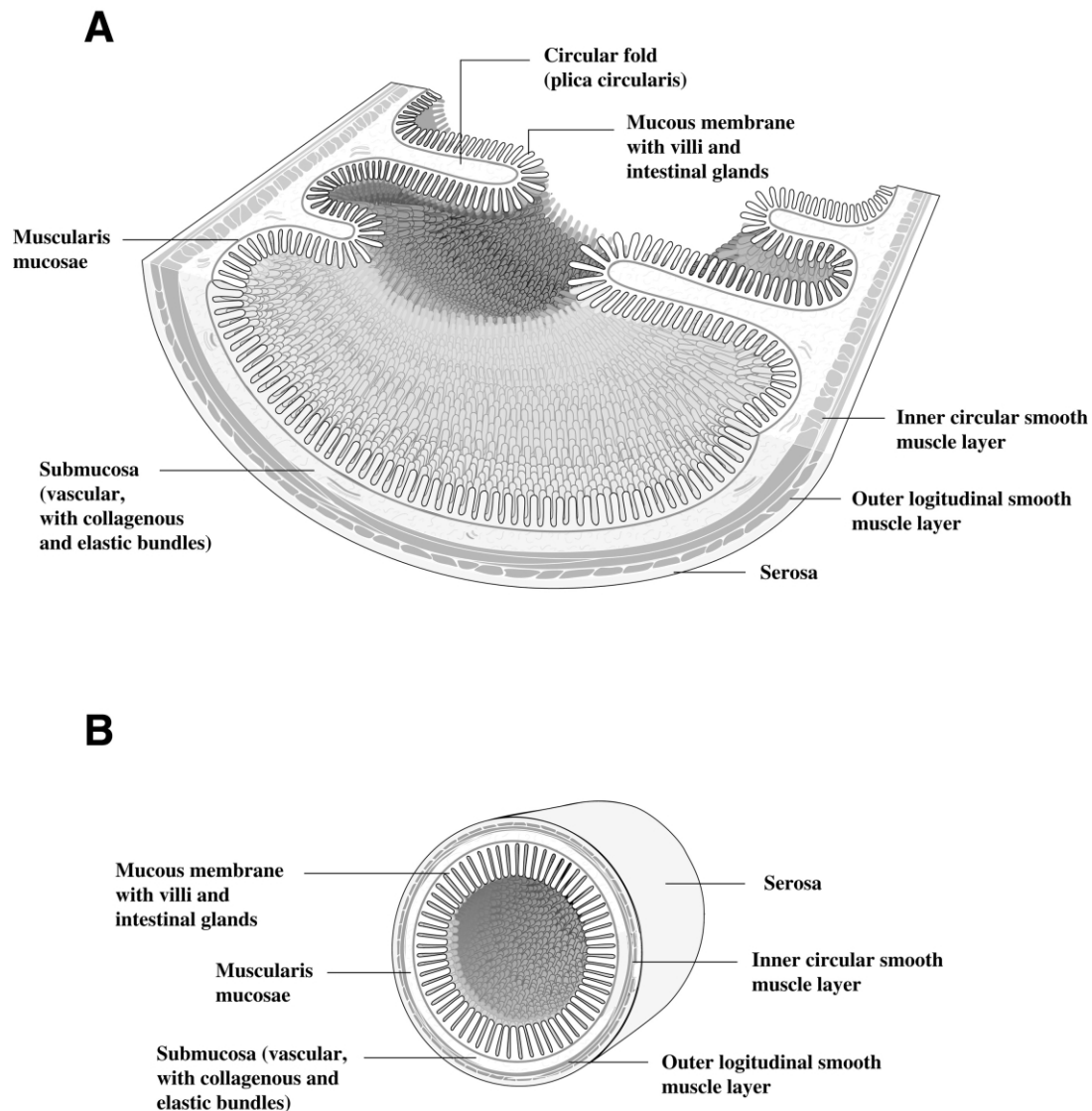


Fig. 4. Cross-sections of the proximal small intestines of humans (A) and rats (B) illustrate luminal surface modifications. The surface areas for absorption from the lumina of the small intestines of rats and humans are greatly increased by the presence of millions of tiny finger-like projections (villi). In the rat (B), which has a thick, chalky chyme, the villi project into the lumen from the cylindrical intestinal wall. In humans (A), which have a watery chyme, the absorptive surface area is further amplified by the presence of folds of luminal epithelium (plicae circulares) that intrude into the lumen, thereby allowing many million more villi to come into contact with chyme. (See also Fig. 9 for a depiction of the difference in blood supplies to areas with many versus few intestinal folds).

and the short duration of time compounds are in contact with the stomach epithelium, compared to that of the intestines. Neither the anatomy of the oral/pharyngeal/esophageal epithelium, nor the relatively short time that food is in contact with the mucosa of those regions is conducive to absorption. A small amount of absorption does occur sublingually (at the underside of the tongue and the floor of the mouth beneath the tongue) and across the buccal membranes; these routes have been exploited for the delivery of certain pharmaceuticals (e.g. nitroglycerin, isosorbide dinitrate) (Murad, 1990).

5. Dimensions and surface areas of the intestinal tract

The primary site of absorption of substances from the lumen of the alimentary canal is the intestinal tract. A comparison of the dimensions of the intestinal tract would therefore seem to be a logical first step in comparing GI absorption in humans and rats. That task, however, is not easily accomplished. There exist few

readily accessible sources of such data for the rat, while the more abundant data for the human vary widely. Table 1 indicates the diversity of information related to the reported lengths of human intestinal regions. The main reasons for such variation are that lengths were measured (1) at different times (i.e. in vivo vs post-mortem) and (2) by different methods. The methods of measurement are rarely described in texts. Snyder et al. (1975) state that physiological lengths obtained from living persons by intubation methods are probably too short due to the gathering of the intestine on the tube and the tendency of the tube to “cut corners,” rather than remain in the center of the lumen. In contrast, anatomical lengths recorded postmortem are too long, because the loss of intestinal smooth muscle tonicity after death results in elongation of the intestinal tract. The true in vivo length ranges between the two.

Table 2 presents a comparison of the anatomical lengths of the intestinal tract and its major subdivisions in humans and rats. [The values for the human were taken from Snyder et al. (1975), a committee report on

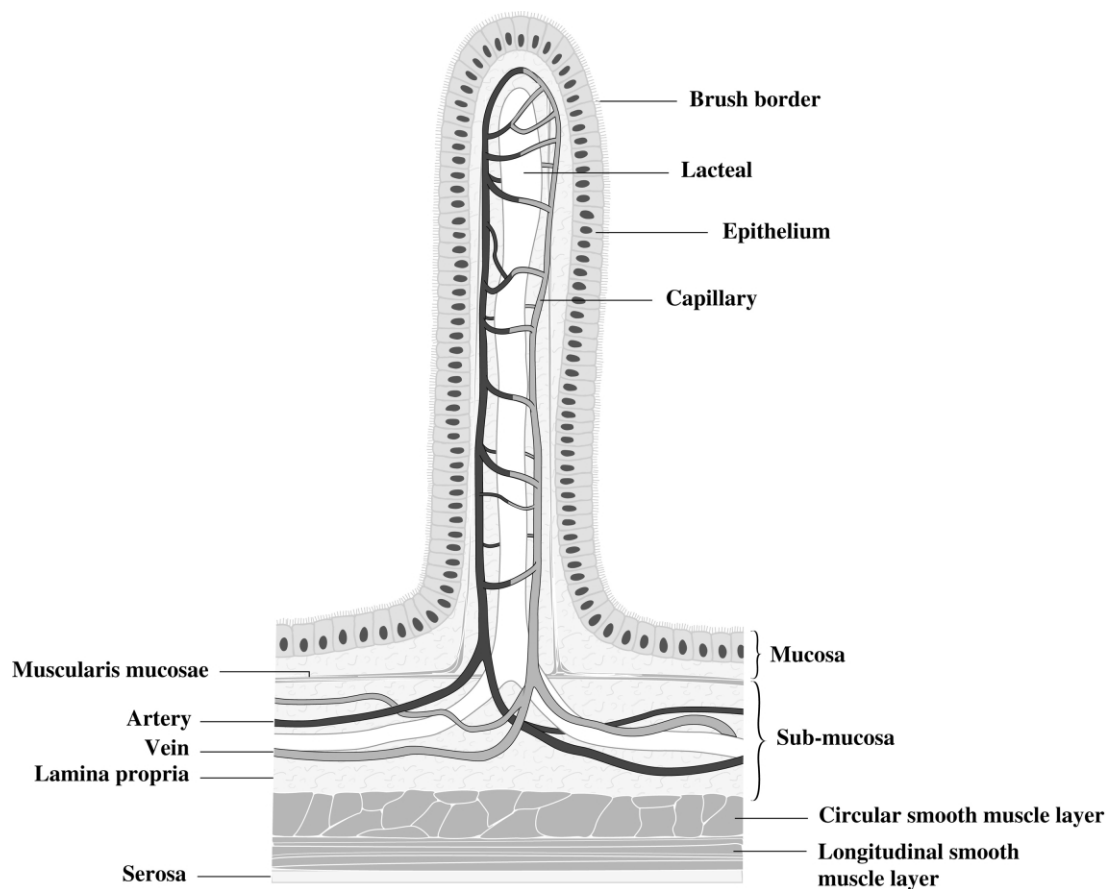


Fig. 5. Diagram of the structure of an intestinal villus. The luminal surface of the entire intestinal tract, including the villus, is lined by enterocytes. Note the fuzzy appearance of the brush border on the surface of the villus. The deep structure of the villus is characterized by a large, blind-ending lymphatic vessel, the lacteal, which is responsible for absorption of higher molecular weight substances, including fats. A small plexus of blood capillaries surrounds the lacteal. In addition to the vascular structures, the villus contains loose connective tissue and small amounts of smooth muscle (muscularis mucosae) which wiggles the villus back and forth in the liquid layer adjacent to the intestinal wall, thereby increasing the efficiency of absorption.

“reference man”; anatomical values are shown so that appropriate comparisons may be made to published data on the rat (Hebel and Stromberg, 1986).] The length of the human intestinal tract is only 5.5 times the length of the rat intestinal tract, despite the much larger body size of the human (70 kg) compared with the rat (0.25 kg). The relative sizes of the subdivisions of the intestinal tracts also differ. In rats, the small intestine comprises 83% of the total length of the intestinal tract, and about 90% of the small intestine is jejunum. The small intestine of humans is 81% of the total intestinal tract length, though only 38% of the small intestine is jejunum. Another outstanding difference between the intestinal tracts of these two species is the relative sizes of the ceca. In rats, the cecum, which is a primary site of microbial digestion (Swenson and Reece, 1993), accounts for approximately 26% of the length of the large intestine, whereas the cecum accounts for only about 5% of the length of the large intestine in humans. Rats lack a sigmoid colon, probably due to differences in the structures of the abdominopelvic cavities between rats and humans [discussed more fully in DeSesso (1995)].

While comparison of the absolute and relative lengths of the subdivisions of the rat and human intestinal tracts reveals some interesting differences between the two species, it does not provide a complete picture of the surface areas available for absorption. Despite the fact that the human small intestine is only about five times the length of the rat small intestine, its surface area is 200 times that of the rat. In humans, three types of anatomical modifications increase the surface area of the small intestine; rats possess only two of these. The

human small intestine possesses numerous, grossly observable folds of mucosa oriented orthogonal to the long axis, like mountain ranges across a prairie (Fig. 4). These plicae circulares (or Kerckring’s folds), which are absent in the rat, increase the surface area by a factor of 3. In both humans and rats, numerous microscopic finger-like projections (villi; Fig. 5) extend from the intestinal wall into the lumen; these increase the surface area by a factor of 5 (rats) or 10 (humans). Human and rat enterocytes also possess thousands of microvilli, which are only visible with an electron microscope and give the appearance of a brush border under light microscopy. Microvilli increase the surface area of the rat and human small intestines by a factor of 20 (Snyder et al., 1975; Granger et al., 1985; Hebel and Stromberg, 1986). In both species these anatomical modifications increase surface area to a greater extent in the duodenum and upper jejunum than in the ileum, that is, the ratio of surface area to length is greater in the proximal region of the small intestine than in the distal region (Snyder et al., 1975; Hebel and Stromberg, 1986). Table 3 presents a comparison of the absolute surface areas for various regions of the GI tract. For both humans and rats, the majority of the surface area is found in the jejunum. In the case of humans, this is due to the plicae circulares in the jejunum; for rats, this is due to the relative length of the jejunum (90% of the small intestine). Modelers may wish to experimentally determine intestinal surface areas; Snipes (1997) provides a detailed methodology for doing so.

Because of the great difference in size between rats and humans, absolute surface areas are not directly comparable; a more meaningful comparison is obtained when the data are normalized for body size. One method for normalizing the data is on the basis of body surface area. Comparison reveals that relative surface area of the human small intestine is more than 4 times that of the rat (Table 3). As the amount of a substance that crosses the enteric mucosa is determined by its flux (amount of mass per unit surface area per unit time), the impact of the increased relative enteric surface area in humans on the comparative absorption of substances is twofold. First, substances that are equally well absorbed in both rats and humans are likely to be absorbed more quickly in humans (i.e. exhibit a higher rate of absorption). Second, substances that are poorly or incompletely absorbed by both species are likely to be absorbed to a greater extent by humans.

It is interesting to note the small absolute surface area of the human stomach (0.053 m²) compared to that of the small intestine (200 m²) (Table 3). This 3800-fold difference in surface areas is one reason why gastric absorption of substances is generally small when compared to enteric absorption. Likewise, based on the modest surface area of the large intestine (0.35 m²), one would anticipate that the large intestine does not favor absorption to the extent that the small intestine does.

Table 3

Comparison of the absolute and relative surface areas of the gastrointestinal tract in humans and rats

Region	Human		Rat	
	Absolute surface area (m ²)	Relative surface area ^a	Absolute surface area (m ²)	Relative surface area ^a
Body	1.8 ^b	–	0.04 ^c	–
Stomach	0.053 ^b	0.029	0.00062 ^d	0.016
Small intestine	200 ^b	111	1 ^e	25
Large intestine	0.35 ^b	0.19	0.034 ^f	0.85

^a Absolute surface area of the intestinal region divided by body surface area.

^b Snyder et al. (1975).

^c Young et al. (1991): surface area in m² = (0.1 × (body weight in kg)^{0.67}); assume a rat body weight of 0.25 kg.

^d Surface area of the glandular stomach; Jarvis and Whitehead (1980).

^e Hebel and Stromberg (1986).

^f Surface area per unit of length from Gutschmidt et al. (1983); lengths from Hebel and Stromberg (1986).

Table 4
Alimentary tract secretions and additional enzymes important for digestion and absorption in humans

Secretions and additional enzymes	Daily secretion volume (l)	Secretion pH	Chief constituents important for digestion/absorption	Function
Saliva — produced and secreted by the salivary glands and released into the mouth and pharynx	1.0–1.5	~6 (basal) ~8 (stimulated)	α -Amylase (ptyalin) Lingual lipase Mucus Epidermal growth factor Antibacterial compounds	Polysaccharides → di/oligosaccharides Triglycerides → mono/diglycerides + free fatty acids Moistens/lubricates food for swallowing, protects epithelium Stimulates growth of gastric mucosa Include peroxidase, lysozyme, and immunoglobulin A
Mucus — produced and secreted by the mucus glands of the esophagus	??	neutral — acidic (location-dependent)	Mucus	Protects epithelium from physical injury
Gastric juice — produced and secreted by the oxyntic and pyloric glands of the stomach	1.5–2.0	1–3	Hydrochloric acid Pepsin(ogen) Intrinsic factor Mucus Bicarbonate	Breaks up particles of food; begins protein digestion; kills bacteria that entered with food; pepsinogen → pepsin Proteins → large polypeptides; pepsinogen → pepsin Necessary for absorption of vitamin B ₁₂ by ileal mucosa Protects epithelium from physical/chemical (acid) injury Immobilized in surface mucus layer: neutralizes acid
Secretions of the Brunner's glands of the proximal small intestine	~0.2	8–8.9	Bicarbonate Mucin Epidermal growth factor	Neutralizes acidic chyme entering duodenum from stomach Protects epithelium from physical/chemical (acid) injury Stimulates growth of intestinal mucosa
Bile — produced by the liver; stored and concentrated in the gall bladder; released into the duodenum	0.5–1.0	7–8	Bile salts Bicarbonate Organic wastes	Solubilize fats; ferry lipids to the mucosa for absorption Neutralizes acidic chyme entering duodenum from stomach Eliminated from the body
Pancreatic juice — produced by the pancreas and released into the duodenum	1–1.5	7–8	Bicarbonate α -Amylase Trypsin(ogen) Chymotrypsin(ogen) (pro)Elastase (pro)Carboxypeptidases Lipase-(pro)colipase (pro)Phospholipase A ₂ Cholesterol esterase Ribonuclease Deoxyribonuclease	Neutralizes acidic chyme entering duodenum from stomach; puts enteric contents at optimal pH for digestive enzymes Polysaccharides → di/oligosaccharides Protein → small peptides; activates pancreatic enzymes Protein → small peptides Protein → small peptides Cleaves amino acids from carboxy terminus of peptides Triglycerides → monoglycerides + free fatty acids Cleaves a free fatty acid from a phospholipid Hydrolyzes esters of cholesterol, vitamin A, and vitamin D Ribonucleic acids → oligoribonucleotides Deoxyribonucleic acids → oligodeoxyribonucleotides
Succus entericus — produced and secreted by epithelial cells of the small intestine	1–2	7.5–8	Mucus Enterokinase?	Lubricates and protects epithelium Trypsinogen → trypsin

(continued on next page)

Table 4 (continued)

Secretions and additional enzymes	Daily secretion volume (l)	Secretion pH	Chief constituents important for digestion/absorption	Function
Enzymes integrated into or adhered to the small intestinal membrane, or enzymes localized within cells of the small intestine; substrates may be metabolized within the cell, or enzymes may be released into the intestinal lumen when cells are exfoliated	–	–	Enterokinase α -Amylase Disaccharidases Aminopeptidases Dipeptidases Intestinal lipase Cholesterol esterase Nucleotidases Nucleosidases	Trypsinogen→trypsin Polysaccharides→di/oligosaccharides Di/oligosaccharides→monosaccharides Cleaves amino acids from amino terminus of peptides Dipeptides→free amino acids Triglycerides→glycerol+ free fatty acids Hydrolyzes esters of cholesterol, vitamin A, and vitamin D Nucleotides→nucleosides+ phosphate Nucleoside→purine/pyrimidine base+ pentose
Enzymes within small and large intestinal cells	–	–	Phase I and II enzymes	Include cytochrome P450, glucuronyltransferase, sulfotransferases, and others: metabolize xenobiotics
Secretions of the large intestinal epithelial cells	~0.2	7.5–8	Mucus	Lubricates and protects epithelium; binds fecal matter
Enzymes of bacteria residing within the lumen of the large intestine	–	–	Bacterial enzymes	Metabolize (especially by reduction and hydrolysis) nutrients, xenobiotics, and phase II conjugates

References: Aungst and Shen (1986); Chhabra and Eastin (1984); Davison (1989); Granger et al. (1985); Guyton and Hall (1996); Hoensch and Schwenk (1984); Jacob and Francone (1970); Jennings (1972); Johnson (1985); Kaminsky and Fasco (1992); Laitinen and Watkins (1986); Langley et al. (1974); Magee and Dalley (1986); Pelkonen and Hänninen (1986); Shepard (1971); Vander et al. (1985); Weiss (1988); Young et al. (1991).

6. Motility and transit time

Most of the alimentary canal of both humans and rats is surrounded by at least two layers of smooth muscle. The muscle fibers of the inner layer are arranged circumferentially relative to the lumen; those of the outer layer are arranged parallel to the long axis of the canal. The co-ordinated, rhythmic contractions of these layers of smooth muscle cause the intestinal motility which is responsible for the thorough mixing of chyme, the continual re juxtaposition of chyme with the brush border of the enterocytes, and the propulsion of food through the GI tract in a net aboral direction (peristalsis). In addition to the external layers of smooth muscle, there is a thin layer of smooth muscle associated with the lamina propria (muscularis mucosae) that causes the intestinal villi to undulate, thereby agitating the layer of fluid (the unstirred layer) that is associated with the brush border of the enterocytes.

Transit time is the amount of time taken for a bolus of food or chyme to traverse a region of the alimentary canal. In the mouth, transit time is determined by voluntary control over the length of time spent in chewing. Once a bolus of food is passed to the pharynx and esophagus, control of transit time is governed by both gravity and primary peristalsis. The total transit time through the human pharynx and esophagus is about 6 sec. Upon reaching the stomach, ingested materials experience

transit times that depend on the nature of their contents (Johnson, 1985; Vander et al., 1985). In the fasted condition, the half-time for saline emptying from the human stomach is 12 min, while the gastric transit time for a meal is about 4 h (Granger et al., 1985). Generally, meals comprised of the various dietary constituents empty from the stomach at varying times with the carbohydrate portion emptying first, protein at an intermediate time, and the fatty part last. Liquids drunk during a meal frequently bypass the solid portions of a meal and enter the duodenum quickly (Granger et al., 1985).

Chyme traverses the human small intestine at a rate of 1–4 cm per min (Granger et al., 1985). The velocity of transport is faster in the proximal portions of the small intestine (duodenum and proximal jejunum) and decreases as chyme approaches the ileum. On average, chyme traverses the entire small intestine in 3–4 h. Transit time for chyme in the human large intestine is considerably slower. Depending on the amount of fiber or other insoluble materials in the diet, transit time through the large intestine in healthy humans is 2–4 days (Granger et al., 1985).

The time for chyme to traverse the small intestine of rats is also approximately 3–4 h. As in the case of humans, the velocity of transport is faster in the proximal segments of the small intestine than in the distal segments (Marcus and Lengemann, 1962). The transit time through the large intestine of rats has been reported to be approxi-

mately 15 h (Enck et al., 1989). It should be noted, however, that the values reported for transit times in both humans and rats are subject to great variations depending on many factors including health status, age and fasting state. For this reason, these values should be determined experimentally for modeling purposes, and published values should not merely be accepted.

Most absorption of substances takes place during the time that chyme is in the small intestine. Absorption of some fluid and electrolytes, as well as products of bacterial digestion of otherwise indigestible materials, takes place while chyme remains in the large intestine. Generally, an

increase in intestinal transit time will increase the absorption of poorly or incompletely absorbed substances. However, this is not always true. For instance, some substances (e.g. anticholinergics) increase transit time by inhibiting intestinal smooth muscle motility. While inhibition of peristalsis does increase intestinal transit time, it also inhibits the movements of the intestine that mix chyme and agitate the unstirred layer of fluid. These movements are especially important for the absorption of lipophilic substances because without them, the unstirred layer forms a barrier between the brush border membrane and the micelles that contain the lipophilic substances.

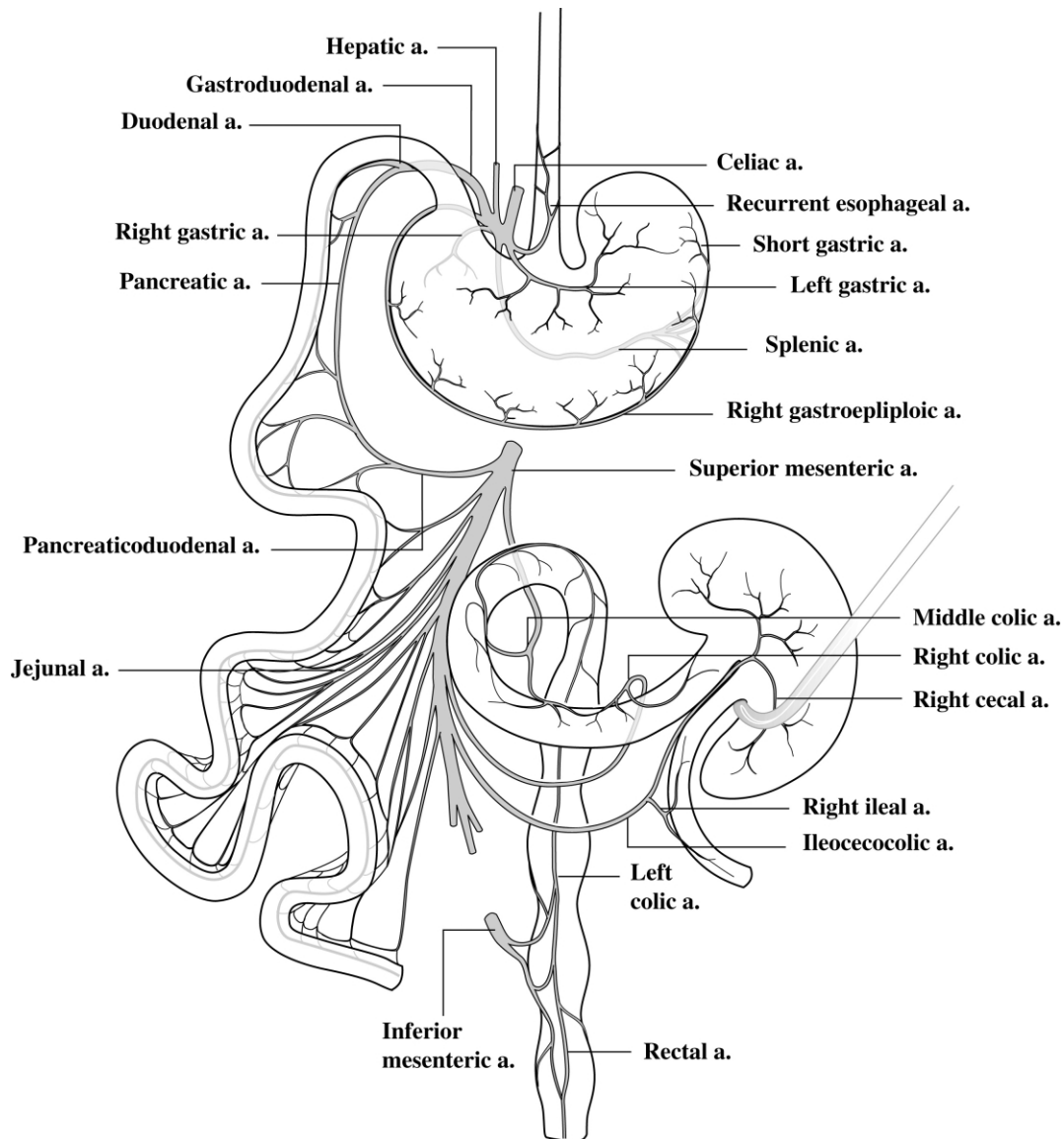


Fig. 6. The arterial blood supply to the rat gastrointestinal tract. The rat arterial pattern is quite similar to that of the human. In both species, blood is provided by three major branches of the aorta: the celiac artery, which supplies the caudal portion of the esophagus, the stomach, the proximal duodenum, and portions of the pancreas; the superior mesenteric artery, which provides blood to portions of the pancreas, the caudal duodenum, the entire jejunum and ileum, the cecum, the ascending colon and the proximal half of the transverse colon; and the inferior mesenteric artery, which furnishes blood to the caudal large intestine and most of the rectum. Note that the arteries to the intestines travel in tissue folds (mesenteries) that connect the intestines to the body wall and they enter the intestines along the margins of the organs.

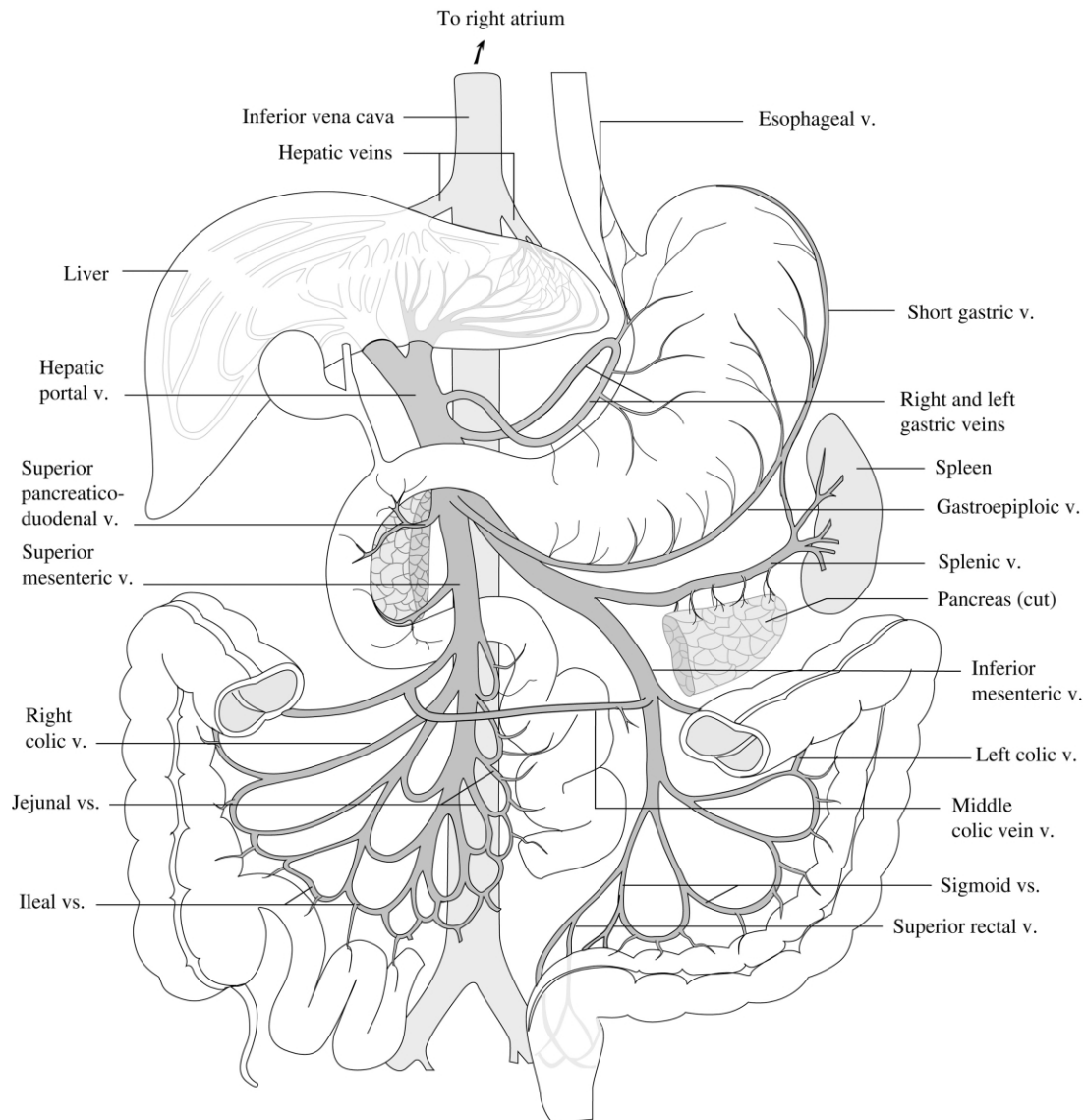


Fig. 7. Diagram of the hepatic portal system of humans. Blood draining from the stomach (via the gastric veins) and the entire small and large intestines (via the superior and inferior mesenteric veins) eventually enters the large hepatic portal vein, which delivers the blood to the liver before the blood returns to the heart by way of the inferior vena cava. This vascular arrangement ensures that all material absorbed into the blood vessels of the gastrointestinal tract passes through the liver, where materials can be removed or metabolized prior to entering the general circulation. This is the anatomical foundation for the phenomenon known as the first-pass effect.

7. The nature of luminal contents

The nature of the luminal contents in both humans and rats is altered as the contents traverse the alimentary canal. This alteration is due to (1) the physical dispersion of ingested solid matter by chewing and the muscular activity of the stomach, coupled with the mixing of the ingested matter with imbibed fluid and digestive juices; (2) the action of enzymes on GI contents; (3) the absorption of fluid and materials from the lumen; and (4) the addition of bacterial flora to the contents. Each of these topics is discussed below.

(1). Table 4 presents a summary of the daily volumes, pHs, and constituents of digestive fluids secreted (under

neuronal and hormonal control) by the various portions of the human digestive tract and adnexal organs. [Although values vary among publications, those in Table 4 may be used as a starting point for modelers. Additional data are summarized in Kararli (1995).] The quantity and characteristics of these secretions can be altered in response to luminal contents. In addition to the intestinal secretions, water can move from the blood into the duodenum in response to a hypertonic meal, in order to maintain the isotonicity of luminal contents with plasma (Granger et al., 1985; Johnson, 1985; Vander et al., 1985).

The pH of the luminal contents is modified by the pH of the various secretions. In most regions of the digestive tract, the secretions are slightly alkaline, and the luminal

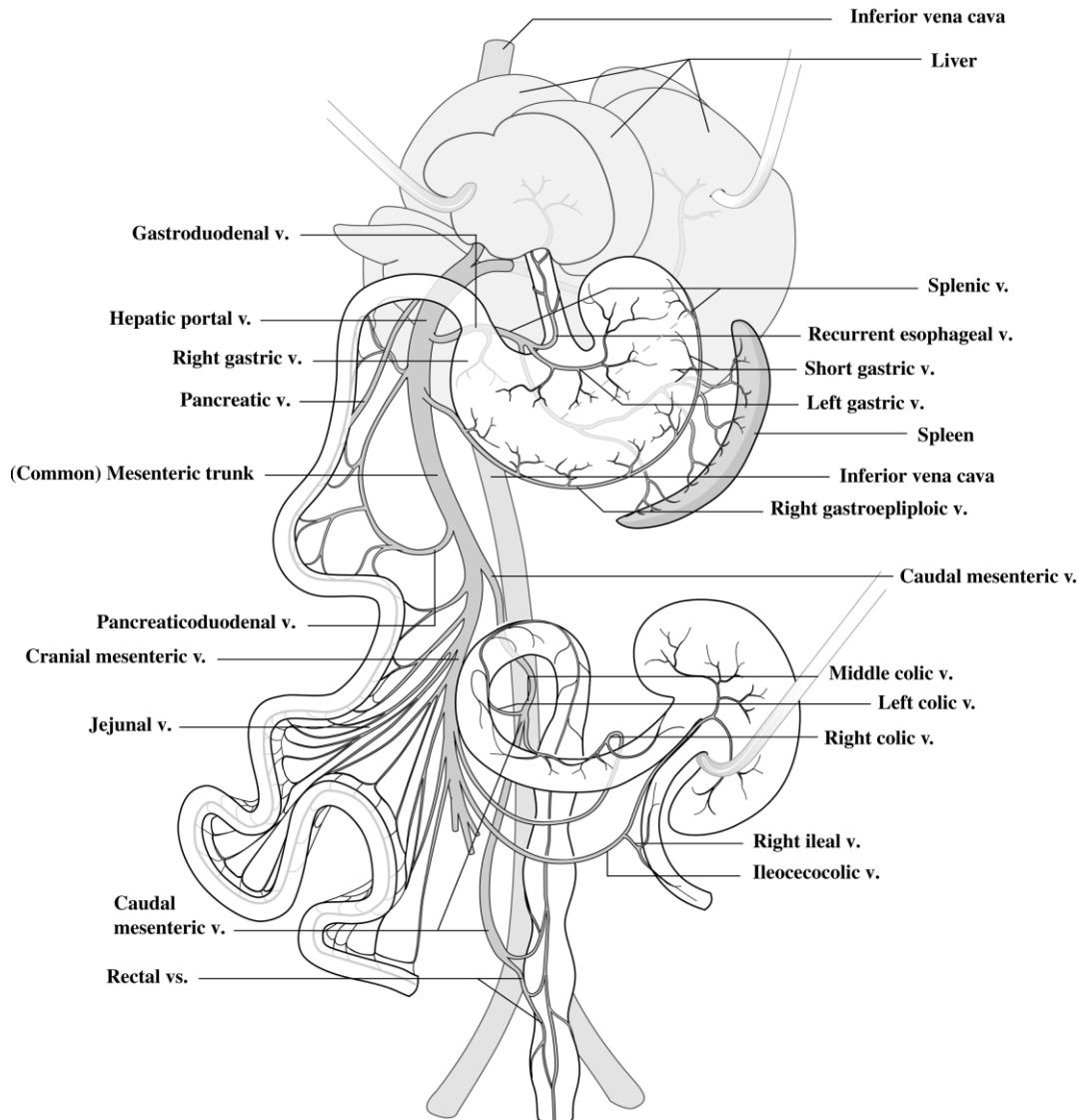


Fig. 8. Diagram of the hepatic portal system of rats. The pattern of venous return from the gastrointestinal tract in rats exhibits some variability; a common pattern is illustrated. In general, the venous return is similar to that of humans in that blood draining from the intestines eventually coalesces into the hepatic portal vein which obligatorily passes through the liver before entering the inferior vena cava. Note that due to the difference in anatomical positions between humans (upright) and rats (prone), the names of the analogous mesenteric veins of the rat are the cranial and caudal (rather than superior and inferior) mesenteric veins.

contents exhibit a pH of 7–8. The stomach is the lone exception to this general statement. The secretion of acid by the gastric mucosa results in acidification of chyme. In humans, the pH of chyme in the stomach may be as low as 1–2; in rats the pH of chyme is less acidic (pH 3–5) (Kararli, 1995). When chyme enters the duodenum, it is quickly neutralized by the alkaline secretion of the Brunner's glands. The pH of chyme affects the ionization state of certain molecules and, therefore, can affect absorption.

With regard to interspecies differences in secretions into the intestinal tract, it is important to make note of an important anatomical difference between rats and humans. Rats lack a gall bladder, the function of which is to store and concentrate the bile that is made con-

tinuously by the liver. This means that, in rats, bile enters the duodenum continuously as it is made. Rat bile is a dilute solution which enters the duodenum in rather copious amounts when compared to the concentrated bile of humans, which is released only when chyme is present. By way of comparison, humans secrete from the gall bladder 2–22 ml bile per kg body weight each day (Dressman and Yamada, 1991), compared with 48 ml bile per kg body weight each day secreted directly from the liver in the rat (Kararli, 1989).

(2). The contents of the alimentary canal are also altered by many enzymes found in the secretions of the digestive tract, integrated into or adhered to the cell surface membrane of small intestinal cells, and present within small intestinal cells (Table 4). Many of these

enzymes work to digest carbohydrates, proteins and fats into readily assimilated molecules necessary to sustain life. Others are involved in the metabolism of xenobiotic compounds. Such compounds may be oxidized, hydrolyzed and conjugated with large, polar molecules in order to facilitate their excretion. In some instances, however, this attempt at detoxification actually produces compounds that are more toxic than their parent compound. The presence and activity of all of these enzymes may vary among species, with age and sex, along the length of the digestive tract and the height of the villus, with time of day and diet, and among individuals (Chhabra and Eastin, 1984; Hoensch and Schwenk, 1984; Laitinen and Watkins, 1986; Kaminsky and Fasco, 1992).

(3). As chyme moves through the GI tract, fluids, electrolytes, nutrients and xenobiotics are absorbed, thus changing the make-up of the remaining luminal contents. In addition, just as water can flow from blood to lumen in the case of hypertonic meals, water can rapidly be absorbed from the gut into the blood after hypotonic meals, again to maintain isotonicity of the luminal contents with plasma. It should be noted that of the 8–9 liters of fluid that enters the human upper digestive tract each day (approx. 1.5 l of ingested fluid plus approx. 7 l of secreted digestive juice), only about 1 l enters the large intestine, and only about 100 ml of water is found in the daily output of feces. Although this demonstrates that the intestines are capable of absorbing large amounts of fluid daily, their maximum absorptive capacity is, in fact, much larger than the total of ingested fluid (Granger et al., 1985; Johnson, 1985; Vander et al., 1985).

The nature of ingesta itself can impact absorption of nutrients and xenobiotics. For instance, diets that are high in fiber tend to (1) sequester some of the poorly soluble and lipophilic substances, making them unavailable for contact with the brush border (Gregus and Klaassen, 1986) and (2) decrease transit time through the intestinal tract (Granger et al., 1985). Both of these tendencies favor decreased absorption from the lumen.

(4). Bacterial flora populate much of the GI tract of both humans and rats and become an ingredient of the luminal contents. The mouth and pharynx have a rich and diversified bacterial population, though it is not important in absorption. In rats, large numbers of microorganisms are found in the stomach and intestines. In humans, however, because of the low pH of gastric contents, microorganisms are virtually absent in the stomach and proximal small intestine; large numbers of bacteria are not encountered until chyme reaches the distal ileum and large intestine (Drasar et al., 1970; Calabrese, 1983; Borriello, 1984; Granger et al., 1985). Bacteria are living organisms capable of metabolizing substances in chyme and thus altering its contents. Differences between humans and rats with regard to the numbers and types of bacteria, as well as to their geographical location

within the digestive tract, affect the site and extent of absorption of some substances (Granger et al., 1985; Pelkonen and Hänninen, 1986). Once chyme has reached the colon, bacteria become a major component of the luminal contents. With the dehydration of chyme that occurs as it traverses the large intestine, bacteria eventually make up over 33% of the dry weight of the luminal contents in the distal human large intestine (Granger et al., 1985).

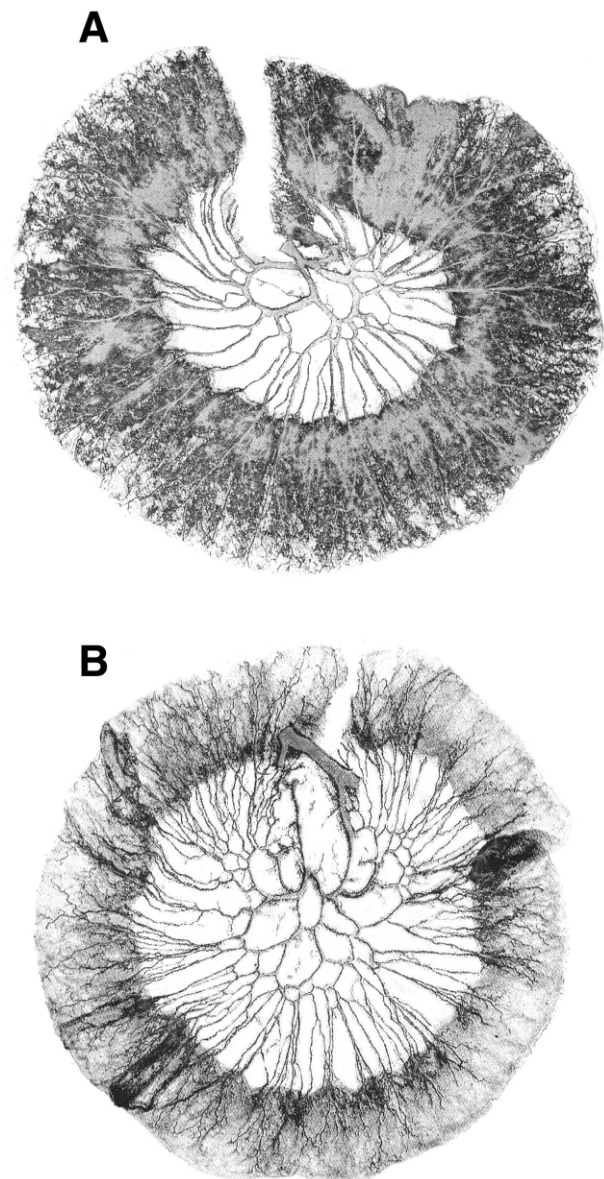


Fig. 9. Depiction of the blood supply in the human proximal jejunum (A) vs the human ileum (B). The vascularity of these segments of the human intestine was visualized by injecting the superior mesenteric artery with colored gelatin, followed by clearing of the tissue in benzene. Note the much greater vascularity in the wall of the jejunum vs that of the ileum, indicating the greater potential for jejunal absorption. This is a consequence of the presence of numerous plicae circulares in the proximal portion of the human small intestine [drawn after a preparation by Dr. Michael C.E. Hutchinson (Warwick and Williams, 1973, p. 1285)].

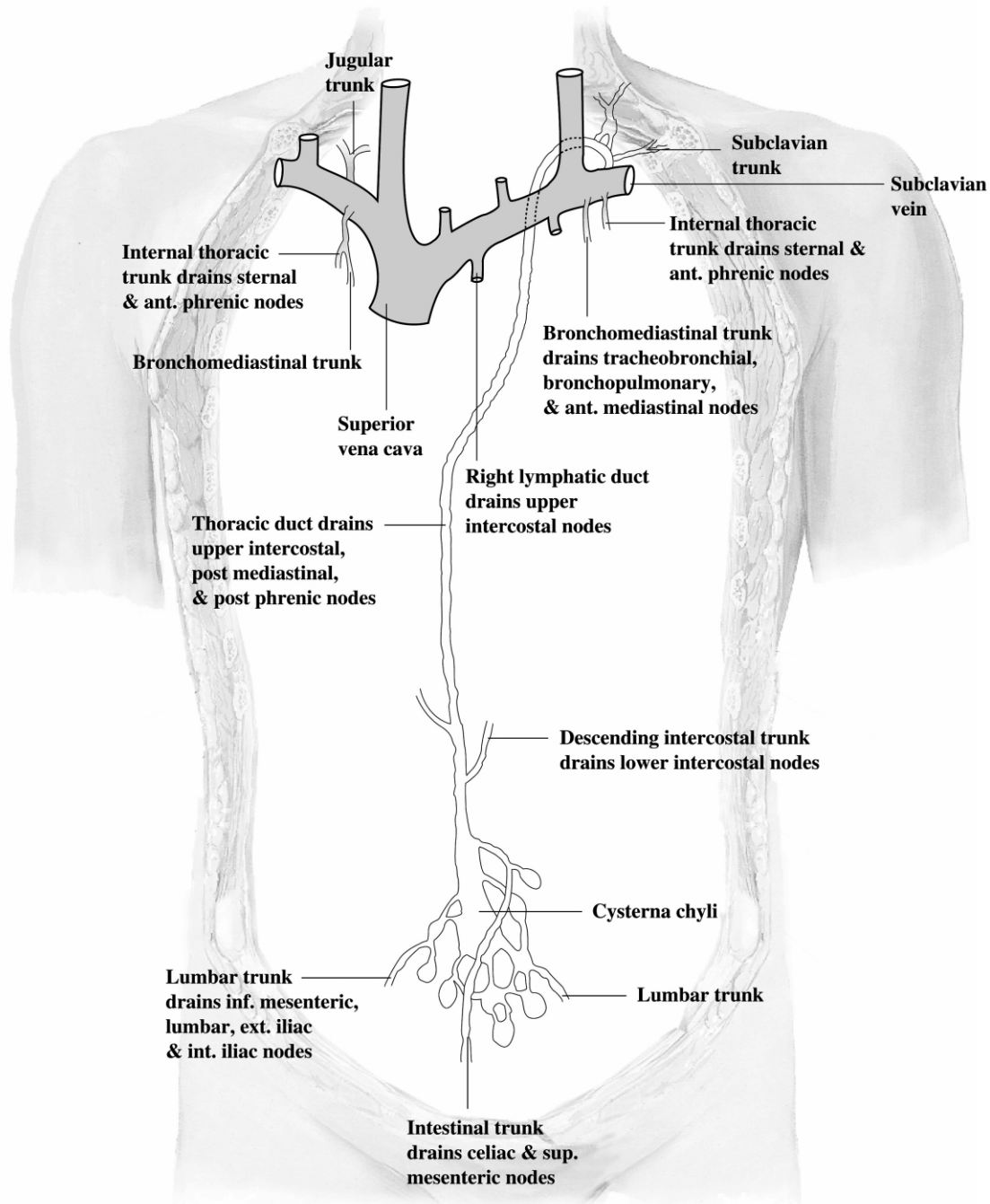


Fig. 10. Arrangement of the human thoracoabdominal lymphatic system. Some high molecular weight and fatty materials absorbed from the intestinal tract make their way into the lacteals and follow the lymph, to eventually enter the general circulation at the point where the left jugular and left subclavian veins join to form the brachiocephalic vein. From this point, the blood and lymph pass directly to the right atrium of the heart. Thus, material absorbed into the lymphatics does not initially pass through the liver and does not undergo first-pass metabolism. Rats have a similar arrangement of lymphatic vessels, and consequently, material absorbed into the rat lymphatic system also avoids first-pass metabolism.

8. Blood and lymph flow

The tissues of the human and rat alimentary canals, like other tissues of the body, contain vessels of both the blood and lymphatic vascular systems. The absorbed material that is transported by both the blood and lymphatic vessels passed through the enterocytes to gain

access to the interstitial fluid of the lamina propria. This interstitial fluid has a dual origin: it is derived both from the fluid that passes out of the lumen of the alimentary canal and also from an exudate of plasma originating from the proximal portions of the capillaries in the lamina propria. This exudate is increased by the physiological hyperemia occurring in the presence of chyme. The

absorbed material moves from the interstitial fluid and into the vessels of the two vascular systems. These vascular systems thus act as a sink: as nutrients move from the interstitia to the vessels, by Le Châtelier's principle, movement from the enterocyte to the interstitia and from the lumen to the enterocyte is favored. This movement depends (1) on the relative fluid flows of the two systems, and (2) on the anatomical arrangement and structure of the vascular beds (see Figs 6–8).

While the rate of perfusion for blood vasculature is about 1000 times that of the lymphatic vasculature for most tissues (Granger et al., 1985), the flow of lymph

from the small intestine is measurable. The resting rate of lymphatic flow in humans is 0.095 ml/min/100 g of intestinal tissue (Jacobson, 1985); this flow rate increases during the physiological hyperemia that occurs after meals. When the intestine is absorbing at near maximum rates, about 20% of the absorbed fluid is transported by the lymphatic vasculature (Jacobson, 1985).

The blood capillaries in the lamina propria of the alimentary canal form a network (plexus) that is located immediately subjacent to the basement membrane of the epithelial layer of enterocytes. The degree of vascularity

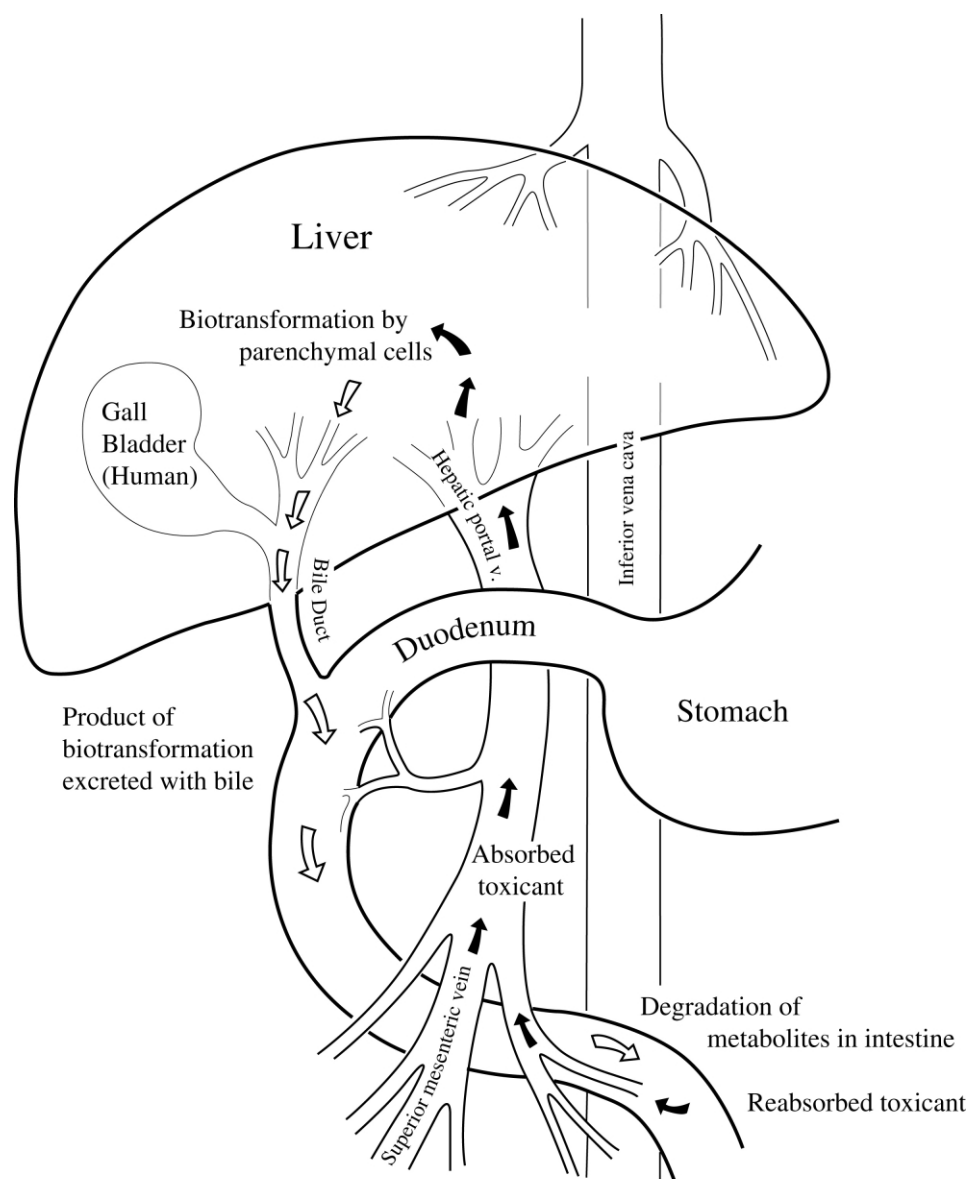


Fig. 11. Enterohepatic recirculation. This schematic depicts the route taken by substances that undergo enterohepatic recirculation. Substances that are absorbed into the blood from the lumen of the small intestine are carried to the liver by the hepatic portal vein (black arrows). Within the liver, compounds can be biotransformed by the hepatic cells. The biotransformed substances are subsequently excreted into the bile and traverse the bile duct to empty back into the lumen of the duodenum (open arrows). There, the substances may be acted upon by digestive enzymes and then reabsorbed into the blood vessels draining the small intestine (black arrow), allowing the preceding steps to be repeated.

of this plexus varies among regions of the GI tract (Fig. 9). The walls of the blood capillaries are formed by a single, thin endothelial cell layer and the basal lamina that surrounds it. The distance between the basement membrane of the enterocytes and the blood capillaries is no more than a few microns. Not only are these vessels located close to the epithelia, but also there are openings in the endothelial cells (fenestrations) that are overlain only by the basal lamina. These fenestrations appear similar to portholes through the cell and serve to expedite the absorption of water and various water-soluble materials. The fenestrations are estimated to be 500 Å in diameter (Bloch and McCuskey, 1973), although proteins as small as albumin (approximately 75 Å diameter) are excluded from absorption, presumably due to the sieving action of the basal lamina.

The lymphatic channels of the alimentary canal (as exemplified by the small intestine) consist of single sac-like vessels (the lacteals) which are located deeper in the lamina propria than the blood capillaries. In the small intestine, the lacteals occupy the centers of the villi; the distance between the basement membrane and the lacteal is estimated to be 50 μ (Jacobson, 1985). The walls of the lymphatic vessels are also comprised of a single endothelial cell layer. However, the lymphatic endothelial cells are thinner than the corresponding blood capillary endothelial cells, there is no overlying basal lamina, and there are no fenestrations. Despite the lack of fenestrations, the lymphatic vessels are permeable to even the largest chylomicrons (emulsion droplets of resynthesized triglycerides, re-esterified cholesterol, and phospholipids formed in and released by enterocytes; approximately 6000 Å diameter) (Granger et al., 1985) due to the presence of permeable spaces (apertures) between adjacent endothelial cells (Weiss, 1973).

These differential routes of absorption for water-soluble materials and chylomicrons lead to the partitioning of absorbed substances between the lymphatic route and the blood vascular route. Substances that are soluble in water (e.g. glucose, amino acids and short-chain fatty acids) follow the blood vascular route; substances with high lipophilicity and low water solubility (e.g. long-chain fatty acids, cholesterol and some xenobiotics) associate with the chylomicrons and therefore follow the lymphatic route (Kararli, 1989; Roth et al., 1993); amphipathic substances with moderate lipophilicity partition between the chylomicrons and the aqueous route (Chhabra and Eastin, 1984; Vander et al., 1985).

Both vascular systems return their contents to the systemic circulation, but they differ with regard to their routes of return. The blood vasculature from the stomach, small intestine and colon coalesce into veins that are tributaries of the hepatic portal vein. All blood from the hepatic portal vein flows into the sinusoids of the liver, where it is in intimate contact with the liver tissue before re-coalescing into one of the hepatic central veins that

drain into the inferior vena cava en route to the heart. Thus, all material absorbed from the stomach, small intestine and large intestine first passes through the liver before entering systemic circulation. Enzymes within the hepatocytes can biotransform nutrients and xenobiotics to compounds either more or less biologically active, concomitantly reducing blood levels of the parent compound. This phenomenon, whereby a toxicant absorbed from the GI tract obligatorily traverses the liver and is subject to hepatic metabolism, is called the first-pass effect.

In contrast, the lymphatic vessels from the stomach and intestines drain into the sac-like cisterna chyli, which is located on the ventral surface of the lumbar vertebral column and is the origin of the thoracic duct (Fig. 10). Lymphatic fluid flows via the thoracic duct to join the venous blood returning to the heart at the juncture of the left subclavian and left internal jugular veins in the root of the neck. This route of return completely bypasses the liver and first-pass metabolism. The first capillary bed traversed by material absorbed into the lymphatic system is in the lungs. Likewise, chemicals absorbed into the blood from the oral cavity (i.e. sublingually or buccally) also bypass this first-pass metabolism and enter the systemic circulation via the jugular veins and the superior vena cava.

9. Enterohepatic recirculation

The hepatic portal system of both humans and rats is comprised of blood flow from the capillaries of the small intestine, through the tributaries of the hepatic portal vein, to the sinusoids of the liver without traversing the heart. Venous blood from the small intestine, which carries absorbed substances, is said to have undergone enterohepatic circulation when it has traversed this route. Once in the liver, many absorbed substances are removed from the blood by the liver parenchymal cells and biotransformed. The products of biotransformation are generally larger and more polar than the parent compounds. These modifications favor excretion into bile, which eventually empties by way of the bile duct into the duodenum. These large, polar molecules tend not to be reabsorbed from the intestine, and the bile therefore serves as a route of excretion into the feces. Certain compounds, however, may be reabsorbed from the GI lumen, either as a result of (usually bacterial) degradation of metabolites in the intestinal lumen or even without biotransformation. Re-entry of these compounds into the enterohepatic circulation may be followed by re-excretion into bile; these two events may cycle a number of times. This process is known as enterohepatic recirculation (Fig. 11), and it can markedly affect the disposition (and, therefore, the effects) of compounds.

If a compound that undergoes enterohepatic recirculation is available for uptake into the systemic circulation, recirculation will maintain its systemic levels, increase its half-life in the blood, and prolong its therapeutic or toxic effects. Alternatively, the compound may remain within the enterohepatic circuit, continually being absorbed from the intestine, taken to the liver, and excreted in bile. In such a case, systemic levels of the compound are low, and effects outside of the GI/enterohepatic tract are diminished, while effects within the tract may be increased (Gregus and Klaassen, 1986).

10. Conclusion

Several parameters require consideration in any attempt (1) to define and model the events involved in GI absorption of nutrients and non-nutrients and (2) to extrapolate the results of these efforts between species. These include anatomical and physiological features of the GI tract (surface area, vascularity, transit time/motility, and enterohepatic recirculation), as well as physicochemical properties of the chemical under study and of the GI contents. Variations in these parameters among different organs of the GI tract and among species could affect the sites and rates of absorption, as well as the distribution and metabolism of the absorbed material. Not all parameters will be important for all chemicals, but a definitive knowledge of the role that each plays in the absorption of a compound of interest should allow a quantitative description of the absorption process. Unfortunately, in many cases the data necessary to evaluate the importance of these parameters is not available, and experiments must be done to measure their effects on absorption. Only by doing so can we effectively understand and accurately model the kinetics of ingested compounds.

Acknowledgements

The authors are indebted to Ms Elaine Mullen for her meticulous attention to detail in the multiple iterations during creation of the figures and to Mr Michael Yang for his assistance in refining the figures to final form. The authors also thank Dr Richard Mavis for his advice in the planning of this project and his stimulating critiques of our early drafts. This work was supported by the US Air Force Armstrong Aerospace Medical Research Laboratory and the Mitretek Biomedical Research Institute.

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