

Physiology of the Mesenteric Circulation

EUGENE D. JACOBSON

Department of Physiology
College of Medicine
University of Cincinnati
Cincinnati, Ohio 45267

The purpose of this educational exercise is to describe some of the salient features of the physiology of the mesenteric circulation, focusing particularly on the regulation of its blood flow. The reader is referred to several recent reviews of the subject that are more extensively referenced with original sources (5, 6, 10, 11). Although the terms "mesenteric circulation" and "splanchnic circulation" are sometimes used synonymously, they are distinct: the mesenteric circulation refers specifically to the vasculature of the intestines, whereas the splanchnic circulation provides blood flow to the entire abdominal portion of the digestive system. In a 70-kg resting adult human male in good health, the major inflow vessel of the mesenteric circulation, the superior mesenteric artery, delivers about 12% of the cardiac output and is therefore unsurpassed in size among all branches of the entire aorta. This vessel supplies the entire small intestine, the proximal half of the colon, and part of the pancreas.

After blood has been distributed by the superior mesenteric artery to the small intestine, it accumulates in the mesenteric veins en route to the great portal vein, which transports the blood to the liver. Since the arterial supply of the liver is provided by the hepatic artery, a branch of another splanchnic vessel (celiac artery), the mesenteric circulation is in parallel with the hepatic artery and in series with the portal vein (Fig. 1). Within the walls of the small intestine the mesenteric circulation is also organized in a manner featuring both in-series and in-parallel relationships. Thus the circulation of the mucosa is in an in-series relationship with the submucosal circulation from which the mucosal vessels arise and is also in an in-parallel relationship with the microcirculation of the muscular layer of the wall. These kinds of relationships permit internal redistribution of blood flow within the organ without altering total blood flow.

The mesenteric microcirculation has three major functional vascular elements (Fig. 2) (1,3). The first category of vessels consists of the microscopic arteries and the arterioles. These vessels have relatively thick walls composed mostly of vascular smooth muscle and are reactive to various stimuli, especially the catecholamines (13). The largest portion of the resistance to blood flow in the entire mesenteric circulation from its origin at the aorta to the portal vein occurs as the blood flows through the microscopic arteries and arterioles; hence they are termed the "resistance vessels" (3). For a drug to increase or decrease blood flow markedly in the mesenteric circulation, the agent must act on the walls of the resistance vessels.

From the arteriole the blood flows into the capillaries located adjacent to the parenchymal cells. Nearly all transport of materials between the blood and the cells takes place at the level of the capillary component of the circulation. Thus O₂, nutrients, and fluids move from the blood into the cells, whereas CO₂, heat, metabolites, and fluids move in the opposite direction. Hence the capillary units have been termed the "exchange vessels" (3). The degree of exchange will depend on the population density of perfused capillaries because only a frac-

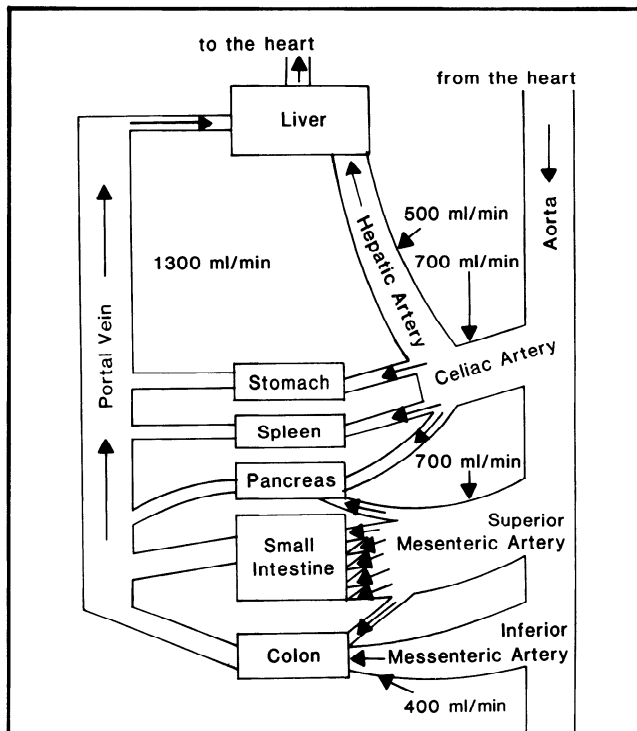


Figure 1
Diagram of splanchnic organs and their blood supply.

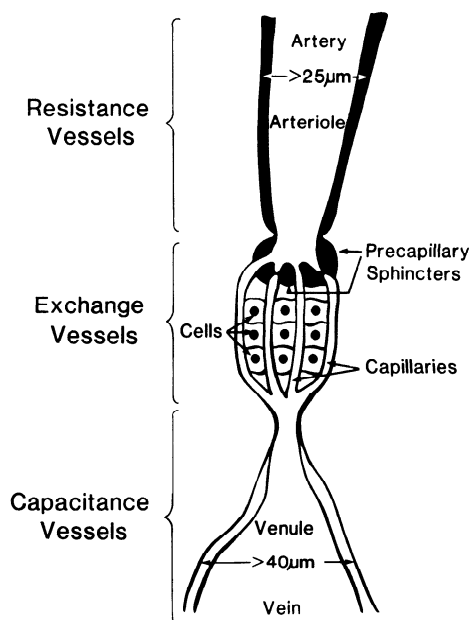


Figure 2
Mesenteric microcirculation. Dimensions represent vessel width below which vessel is termed an arteriole (25µm), as opposed to a microscopic artery, or venule (40µm), as opposed to a microscopic vein.

tion of all capillaries is open to the flow of blood at any moment in time (4). The structure regulating blood flow through the individual capillary is a smooth muscle thickening around the origin of the microvessel. This thickening has been termed the "precapillary sphincter." When this sphincter contracts it closes off the capillary to the flow of blood and thereby reduces exchange between blood in that capillary and adjacent cells. When the sphincter relaxes from the contracted state, the capillary is again perfused with blood, thereby accelerating the exchange. The open capillaries at any moment in time are also referred to as the "nutrient circulation."

The third functionally important component of the mesenteric microcirculation is the microscopic veins that drain the blood from the capillaries. The thin walls of these low-pressure vessels also contain smooth muscle and are responsive to extrinsic stimuli. When their walls contract, blood is expressed centrally from the veins. Since 80% of the total blood in the mesenteric circulation is stored in these microscopic veins, contraction of their walls propels previously stored blood back to the heart, as occurs at the outset of exercise. Because of this storage function the venules have been referred to as "capacitance vessels" (3).

The major categories of regulators of mesenteric blood flow include central cardiovascular control, autonomic neuroregulators, neurohumoral substances, local metabolic factors, and intrinsic vascular properties (Fig. 3). The central cardiovascular regulators are those forces and their relationships that we understand under the rubrics of cardiac output, systemic arterial blood pressure, venous return, and blood volume. Any marked change in these central functions will be reflected by a change in mesenteric blood flow. Thus, for example, if an individual sustains a severe hemorrhage, with decreases in blood volume, venous return to the heart, cardiac output, and arterial pressure, it is hardly surprising that there will also be a decrease in mesenteric blood flow.

The autonomic neuroregulators consist of the sympathetic and parasympathetic nervous systems. The

sympathetic postganglionic vasomotor fibers are distributed along with the branches of the superior mesenteric artery, and the nerves terminate on the vascular smooth muscle of the microscopic arteries, arterioles, venules, and microscopic veins, where they release predominantly norepinephrine.

The results of sympathetic stimulation are a transient decline in blood flow through the mesenteric circulation and a mobilization of blood from the capacitance vessels. The parasympathetic nervous system distributes its postganglionic fibers to this region, but these nerves are not directly vasomotor in character; rather they release acetylcholine near parenchymal cells, resulting in the activation of visceral muscle and secretory units. The result is an increase in motility and secretion that may contribute modestly to an increase in blood flow. Acetylcholine is a vasodilator agent when infused directly into the mesenteric circulation, although it is unlikely that this neurotransmitter actually reaches the vascular smooth muscle of the gut as a result of nerve stimulation.

There are two groups of neurohumoral substances that may have effects on mesenteric blood flow depending on the conditions which have increased the concentrations of these blood-borne substances within the mesenteric circulation. The first group includes the classical vasoconstrictor agents of the body. With stresses such as severe exercise, the plasma concentrations of catecholamines will rise and evoke an increase in vascular resistance. In disease states, such as circulatory shock or congestive cardiac failure, the circulating levels of angiotensin II and vasopressin will increase, again provoking vasoconstriction with a reduction in mesenteric blood flow. The second group of blood-borne materials is the gastrointestinal hormones that are released under more physiological conditions. These peptides have no effect on the smooth muscle of resistance vessels in their usual concentrations, such as those found following the ingestion of a meal. However, these humoral agents do stimulate an increase in motility and exocrine secretion, thereby increasing metabolic need for blood flow to the gut.

Another category of regulators consists of local metabolic factors that are part of the changing metabolic environment near vascular smooth muscle which occurs when the oxidative metabolism of parenchymal cells undergoes an increase. The changes include a decrease in the P_{O_2} as the cells consume more O_2 , an increase in the production of metabolites such as CO_2 , and increased production of paracrine substances such as prostaglandins, adenosine, histamine, and bradykinin. These changes in the metabolic environment cause relaxation of vascular smooth muscle with a reduction in vascular resistance and an increase in mesenteric blood flow. Generally the effect is more marked on exchange parameters that are governed by relaxation of precapillary sphincters than on parameters that reflect relaxation of the smooth muscle of the resistance vessels; thus the increases in O_2 consumption and extraction proportionately exceed the increase in blood flow, and the decrease in mesenteric vascular resistance is usually small (7).

The sequence of events that take place during the stimulation of metabolism in the gut is represented in Fig. 4. When the intestinal lumen contains a solution containing sodium and glucose or sodium and amino

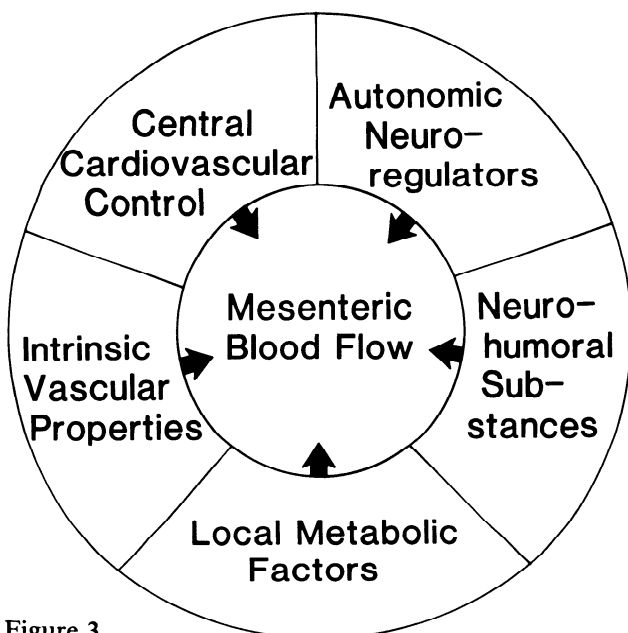
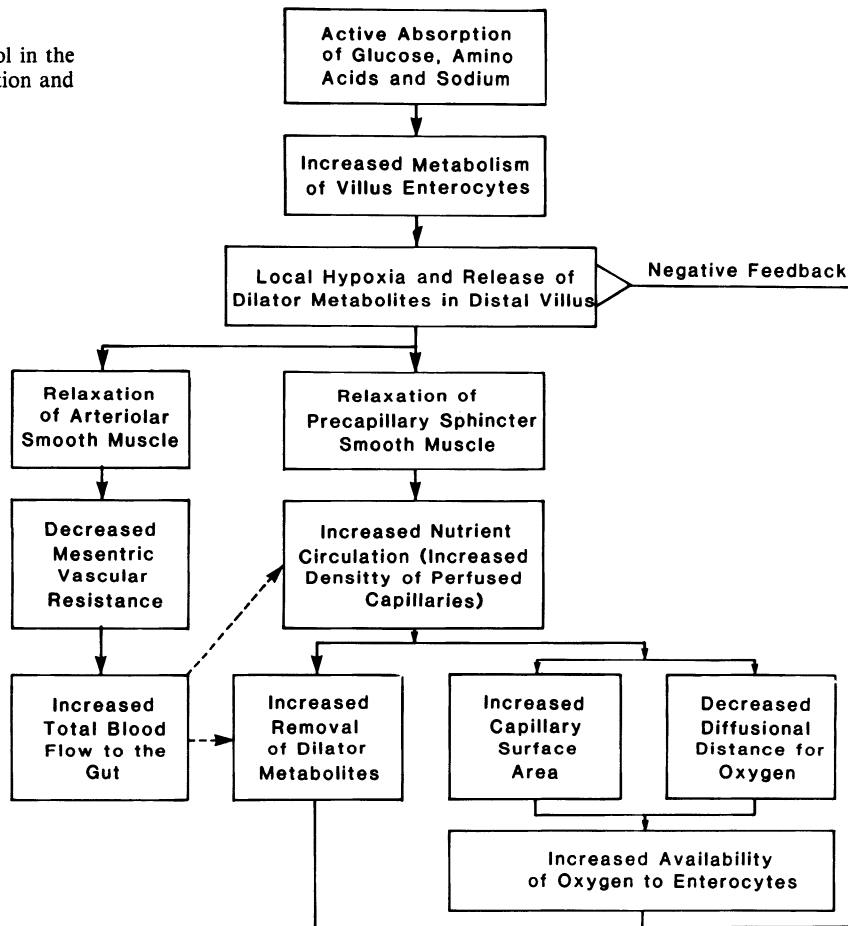


Figure 3
Regulators of mesenteric blood flow.

Figure 4

Metabolic feedback control in the gut: a coupling of absorption and blood flow.



acids, active cotransport of these solutes from the lumen is initiated. This functional activation is paralleled by increased metabolism of the mature enterocytes in the distal villus. The result is an increase in the consumption of O_2 and the release of dilator metabolites from the activated cells. These changes in the metabolic environment relax the precapillary sphincters, thereby causing an increase in the density of perfused capillaries. At the same time there is some relaxation of arteriolar smooth muscle that decreases vascular resistance and leads to an increase in total blood flow through the gut. With recruitment of more capillaries receiving more blood flow, there is an increased removal of the accumulated metabolites. Because of the increased surface area available for diffusion of O_2 and the shorter diffusional distance, more O_2 becomes available for the enterocytes. As a result a negative feedback come into play, which restores the tone of the sphincteric muscle and decreases the perfusion of capillaries. This cycle of ebb and flow through the nutrient circulation is reenacted repeatedly so long as the enterocytes are actively absorbing solutes and placing an increased metabolic demand on the circulation for continued support.

The final category of regulators of the mesenteric circulation the intrinsic vascular properties of this circulation, some of which are fairly unique. One of these characteristics is called "escape" and can be seen during continuous sympathetic stimulation, infusion of catecholamines, or angiotensin II (3, 9). When continuous constrictor stimulation is started, there is a sharp initial decrease in blood flow, but this decrease is transient and the flow returns considerably toward the

control value despite continuous constrictor input. Increasing the degree of continuous constrictor influence again causes a transient but smaller decrease in flow, which again subsides despite the continuous presence of the constrictor influence. The mechanism underlying escape is uncertain, although there is evidence for the release of a dilator intermediary, such as histamine, in response to the decrease in blood flow.

The mesenteric circulation exhibits autoregulation of blood flow in the face of changes in arterial pressure. Autoregulation in the gut is less pronounced than in either the kidney or brain. Within the wall of the small intestine there are both autoregulatory vessels and vessels that display a passive response to changes in intravascular pressure. In the muscularis, vessels that exhibit the passive response are those in which some of the kinetic energy represented by the increase in pressure is expended in overcoming the compliance of the walls of the vessel. As a result there is stretch of the vascular wall with an increase in the internal cross-sectional area of the vessel and a decrease in vascular resistance as the pressure rises. The result is that the increased driving head of pressure meets with a lower resistance and the increase in blood flow is proportionately greater than the increase in blood pressure. By contrast, in the autoregulating blood vessels of the mucosa the increase in blood pressure is met with by active contraction of vascular smooth muscle and a reduction in cross-sectional area. This causes an increase in vascular resistance. Thus the increase in the driving head of pressure results in an increase in blood flow that is proportionately less than the increase in pressure. Autoregulation guarantees better control of blood flow,

which is conducive to the maintenance of a steady tissue O₂ uptake. Interestingly, autoregulation of intestinal blood flow is enhanced by feeding.

Two major theories have been summoned to explain autoregulatory phenomena in the circulation. One, termed the "myogenic theory," assumes that the increase in transmural pressure across the wall of the artery (which occurs when the blood pressure is transiently raised) evokes an active contractile response from vascular smooth muscle of autoregulating circulations. The second, "metabolic theory" assumes that decreased tissue perfusion which occurs when there is a transient fall in blood flow evokes a feedback signal to relax precapillary vascular smooth muscle, thereby overcoming the vascular insufficiency. Both proposed mechanisms appear to operate. The identity of the chemical mediators that contract or relax vascular smooth muscle in autoregulation is unknown, although some evidence points to histamine.

The villi are metabolically the most active portion of the entire intestinal wall. These fingerlike structures project into the lumen of the gut and are responsible for the active cotransport of sodium and nutrients. The configuration of the villus and its microcirculation is conducive to countercurrent exchange (3, 11). Depending on the species of animal, the organization of the villus circulation consists of one or more inflow arterioles, which give off capillaries, usually in a fountainlike distribution at the tip of the villus. The capillaries direct blood flow away from the tip toward the base of the villus and empty into one or more venules, which drain the blood away. The arteriole is situated within 20 μm of capillaries, and the venules and the directions of blood flow in these vessels are countercurrent. Therefore, it is possible for a dissolved substance that is lipid soluble and is present in a higher concentration in the arteriole than in the capillaries or venule to be shunted from the arteriole to the other

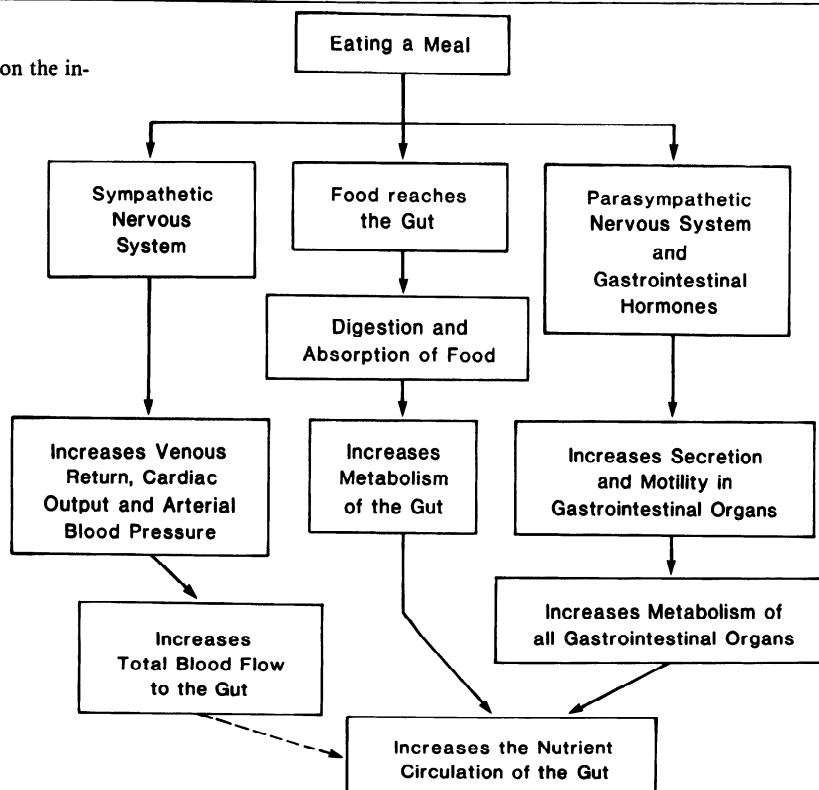
vessels. O₂ is one such substance. Some of the physically dissolved O₂ in the plasma can diffuse from the arteriole to the venule at the base of the villus. As a result of the PO₂ is about 25 mmHg greater at the base than at the tip of the villus (2). This O₂ gradient may contribute to the rapid turnover of epithelial cells in the mucosa. These cells arise in the crypts at the base and migrate over the surface of the villus to the tip, where they die and are sloughed into the lumen. This process of birth to demise of epithelial cells has a half-life of 24 h. When the flow of blood through the villi is slowed by a pathological condition, such as nonocclusive intestinal ischemia, there is amplification of the countercurrent exchanger for O₂ and the first area to suffer necrosis during persistent ischemia is the tip of the villus.

Let us consider several integrating experiences that may confront the mesenteric circulation. The first of these is a frequent occurrence and is physiological, namely the eating of a meal (Fig. 5). The events surrounding eating are stimulating to various areas of the brain and initiate sympathetic nervous responses that constrict the capacitance vessels of the gut and enhance venous return, cardiac output, and arterial pressure. These result in an increase in total blood flow to the gut. Simultaneously, parasympathetic nervous stimulation and the release of gastrointestinal hormones increase exocrine secretion and motility in the gut. This enhanced functional activity leads to increased metabolism of the intestinal parenchyma, which requires an increase in the nutrient circulation for its support. Following ingestion, the food reaches the gut, where the processes of digestion and absorption occur. Again these increases in intestinal function increase metabolism of the enterocytes and also result in augmentation of the nutrient circulation.

Another integrating event, although pathological, is the effect of acute hemorrhage on the mesenteric circulation. If the degree of hemorrhage is not overwhelm-

Figure 5

Effects of eating a meal on the intestinal circulation.



ing, there will be compensations involving abdominal viscera, among other organs, which permit restoration of hemodynamic parameters to normal despite the oligemic insult. With acute blood loss there is a decrease in the circulating blood volume and a decline in the venous return to the heart. The result is a fall in both cardiac output and arterial blood pressure. This signals the activation of a variety of short-term and long-term compensatory mechanisms. Among the long-term processes are shifts of fluid between bodily compartments with fluid moving from intracellular to extracellular spaces and fluid moving from the interstitium into the vascular compartment. The kidney will reabsorb sodium more avidly to increase the return of fluid to the circulation. The shorter-term events include sympathetic nervous stimulation and release of constrictor agents into the circulation, resulting in venoconstriction with mobilization of stored blood from capacitance vessels in the intestine, liver, spleen, and gut and a subsequent increase in the venous return to the heart. As the heart rate and force of contraction are stimulated by the sympathetic nervous system and as the flow of blood from the veins grows, there is an increase in the cardiac output. Sympathetic constriction also acts on the resistance vessels of the splanchnic organs and elsewhere to restore systemic arterial pressure. If the degree of hemorrhage has not been great, these compensatory mechanisms operate within a matter of minutes to restore the arterial pressure and cardiac output to the prehemorrhage levels.

The third example of an integrating experience in the regulation of mesenteric blood flow involves the response to pharmacological agents that either increase or decrease mesenteric blood flow. There are a numerous dilator and constrictor chemicals that have been synthesized and utilized in this circulation, either experimentally or therapeutically, to manipulate blood flow.

In addition, there are numerous naturally occurring substances that influence blood flow to the gut (Table 1). One of the more thoroughly studied intestinal dilator agents is histamine (8). This amine has two types of

vascular receptors, namely the H₁ and the H₂, each of which will bind histamine. For each of these receptors chemists have synthesized selective agonists and antagonists. These receptors mediate separate intestinal dilator responses to histamine, with the H₁ prompting a transient increase in mesenteric blood flow and the H₂ mediating a less intense but longer lasting hyperemia.

Prostaglandins of the A, D, E, and I types are potent vasodilators in the gut (11). In particular, prostacyclin has a potency such that a dose of 10 nanograms per kilogram-minute directly infused into the mesenteric circulation of a dog will increase blood flow significantly (7). Among synthetic vasodilator agents the calcium antagonist drugs are effective in the mesenteric circulation and have been found to interfere with both the slow inward diffusion of calcium into the smooth muscle cell and the intracellular release of calcium (12).

Constrictor agents that have been employed therapeutically to control gastrointestinal hemorrhage include vasopressin, norepinephrine, and angiotensin II.

The existence of a multiplicity of regulatory mechanisms in the mesenteric circulation provides overlapping controls and restricts radical changes in tissue perfusion. This permits moment-to-moment stability in the circulation that favors a steady tissue economy. On the other hand, it is possible with appropriate physiological stimuli, such as eating or exercise, stress states, and drugs, to modify the flow of blood into the gut. We are likely to see the development of more powerful chemical and other approaches to the external manipulation of this blood flow for the benefit of patients suffering from ischemic diseases or hemorrhage.

References

- Berne, R. M., and M. N. Levy. *Cardiovascular Physiology*. St. Louis, MO: Mosby, 1967.
- Bohlen, H. G. Intestinal tissue Po₂ and microvascular response during glucose exposure. *Am. J. Physiol.* 238 (*Heart Circ. Physiol.* 7): H164-H171, 1980.
- Folkow, B. Regional adjustments of intestinal blood flow. *Gastroenterology* 52: 423-431, 1967.
- Folkow, B., O. Lundgren, and I. Wallentin. Studies on the relationship between flow resistance, capillary filtration coefficient and regional blood volume in the intestine of the cat. *Acta Physiol. Scand.* 57: 270-283, 1963.
- Granger, D. N. P. D. I. Richardson, P. R. Kvietys, and N. A. Mortillaro. Intestinal blood flow. *Gastroenterology* 78: 837-863, 1980.
- Mailman, D. Relationships between intestinal absorption and hemodynamics. *Annu. Rev. Physiol.* 44: 43-55, 1982.
- Pawlik, W. W., J. D. Fondacaro, and E. D. Jacobson. Metabolic hyperemia in the canine gut. *Am. J. Physiol.* 239 (*Gastrointest. Liver Physiol.* 2): G12-G17, 1980.
- Pawlik, W., L. L. Tague, B. L. Tepperman, T. A. Miller, and E. D. Jacobson. Histamine H₁- and H₂-receptor vasodilation of canine intestinal circulation. *Am. J. Physiol.* 233 (*Endocrinol. Metab. Gastrointest. Physiol.* 1): E219-E224, 1977.
- Shehadeh, Z., W. E. Price, and E. D. Jacobson. Effects of vasoactive agents on intestinal blood flow and motility in the dog. *Am. J. Physiol.* 216: 386-392, 1969.
- Shepherd A. P. Local control of intestinal oxygenation and blood flow. *Annu. Rev. Physiol.* 44: 13-27, 1982.
- Tepperman, B. L., and E. D. Jacobson. Mesenteric circulation. In: *Physiology of the Gastrointestinal Tract*, edited by L. R. Johnson. New York: Raven, 1981.
- Walus, K. M., J. D. Fondacaro, and E. D. Jacobson. Effects of calcium and its antagonists on the canine mesenteric circulation. *Circ. Res.* 48: 692-706, 1981.
- Zweifach, B. W. *Functional Behavior of the Microcirculation*. Springfield, IL: Thomas, 1961.

Table 1
Drugs Affecting Mesenteric Blood Flow

<i>Dilator Drugs</i>	
Amines	Histamine, H ₁ -receptor agonists (2-methylhistamine), H ₂ -receptor agonists (dimaprit, impromidine)
Peptides	Glucagon, bradykinin
Prostaglandins	A, D, E, and I types
Nucleotides	Adenosine, cAMP, ATP
Cholinergics	Acetylcholine
β-Adrenergics	Isoproterenol
Calcium antagonists	Diltiazem, verapamil, nifedipine
Endorphins	Met-enkephalin
<i>Constrictor Drugs</i>	
Amines	5-Hydroxytryptamine (serotonin)
Peptides	Angiotensin II, vasopressin
Prostaglandins	F _{2α} , tromboxanes
Prostaglandin synthesis inhibitors	Indomethacin
α-Adrenergics	Norepinephrine