LOCAL INTESTINAL HYPEREMIA DUE TO LUMINAL PRESENCE OF FOOD OF DIFFERENT CONCENTRATIONS

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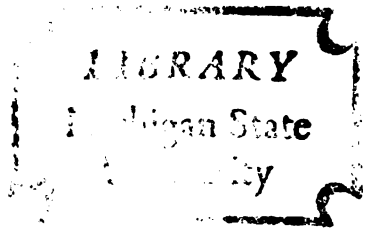

ABSTRACT

LOCAL INTESTINAL HYPEREMIA DUE
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By

Peter R. Kvietys

It has been hypothesized that the postprandial intestinal hyperemia may be restricted to that portion of the intestine directly in contact with food. The purpose of the present study was twofold: 1) to further assess the hypothesis that the intestinal hyperemia produced by the luminal presence of digested food is a local phenomenon and 2) to examine the effects of the concentration (and/or tonicity) of the food in the lumen on the local hyperemia and intestinal motility. To meet this purpose two different surgical preparations of anesthetized dogs were used.

In one preparation the blood flows through the superior mesenteric artery (SMA) and an isolated jejunal segment were simultaneously measured by electromagnetic flowmeter and timed collections of venous outflow respectively during two experimental procedures: 1) Infusion of undiluted digested dog food through the lumen of the duodenal-jejunal portion of the intestine at 4 cc/min for one hour, while the isolated jejunal segment had no contact

with food, and 2) Intraluminal placement of undiluted digested dog food into the isolated jejunal segment for fifteen minutes while the duodenal-jejunal portion of the intestine was left intact.

During the perfusion of the duodenal-jejunal portion of the intestine with food, SMA flow increased while the venous outflow from the isolated jejunal segment did not change. The intraluminal placement of digested food into the jejunal segment, on the other hand, increased the venous outflow of the segment but did not alter the SMA flow.

In another preparation, the venous outflows and luminal pressures (basal and phasic) of two naturally perfused in situ jejunal segments were simultaneously measured while undiluted or diluted (1:2, 1:4, or 1:9 with distilled water) digested food was placed in the lumen of one segment and normal saline in the other segment. The segment containing normal saline served as a control for the segment containing food. As an indicator of the osmolality of the digested food in the lumen, the osmolality of the venous outflow and changes in the volume of the placed food or normal saline were also measured. Furthermore, the four digested food mixtures were centrifuged and the osmolalities of the supernatants were determined in vitro.

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The luminal placement of undiluted digested food, 1:2, 1:4, or 1:9 food increased the venous outflow of the segment containing food, but did not affect the venous outflow of the control segment. As compared to the changes in the venous outflow occurring in the control segment, the magnitude of the increased venous outflow from the segment containing food was similar whether undiluted or any of the diluted foods was present in the lumen. Luminal presence of undiluted food increased the venous osmolality, phasic and basal luminal pressures and the volume of the placed food. Luminal presence of the 1:2, 1:4, or 1:9 diluted food did not alter venous osmolality or luminal pressure; the volume of the placed food, however, was decreased. The decrease in the placed volume of the 1:2, or 1:4 diluted food was comparable to the decrease in the placed volume of normal saline. The decrease in the placed volume of the 1:9 diluted food was greater than the decrease in the placed volume of normal saline. *In vitro* the osmolalities of the supernatants of centrifuged undiluted, 1:2 diluted, 1:4 diluted and 1:9 diluted foods were approximately 1100, 331, 203, and 108 mOsm/kg respectively. *In vivo* the direction and magnitude of the changes in the placed volumes and venous osmolality indicate that, in the lumen, undiluted food is hypertonic, 1:2 diluted food is nearly isotonic,

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To my parents and my wife, Kathryn

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CHAPTER I

INTRODUCTION

Virtually all of the existing evidence suggest that the blood flow to the splanchnic viscera increases after a meal in man (4, 10), primates (54), dogs (7, 8, 29, 30, 36, 37, 54-56), and rats (43). Only one study indicates that the superior mesenteric artery blood flow remains unchanged after a meal in dogs (45).

Prior to the mid 1960s, it was generally accepted that the postprandial splanchnic hyperemia was a result of an increase in the cardiac output. This concept was based primarily on indirect measurements of the postprandial cardiac output and regional blood flow in man, dogs, and rats. Measurements of cardiac output using gas equilibrium, dye dilution, or balistocardiogram methods indicated that the cardiac output increases by 25-45 percent during the digestion of a meal (3, 24, 26, 31, 33, 42-44, 50). Measurements of regional blood flow using plethysmographic, thermostromuhr, and K^{42} distribution methods indicated that blood flow to the extremities, heart, kidneys, and brain also increases after meals (1, 28, 37, 43).

Since the mid 1960s, the above concept has been challenged by direct measurements of cardiac output and blood flows to various organs in the body. Measurements of aortic root flow with ultrasonic and electromagnetic flowmeters indicate that the cardiac output during digestion of a meal is unchanged from the fasting value (7, 8, 29, 54-56). Measurements of regional blood flow with flowmeters indicate that, as compared to fasting levels, the blood flows through the renal and coronary arteries are unchanged, whereas, flows through the brachiocephalic and iliac arteries are decreased during digestion (29, 54, 56). These studies indicate that during digestion the increased splanchnic blood flow is due to a redistribution of the cardiac output at the expense of the flow to the extremities.

Blood flow distribution within the splanchnic vascular bed during digestion also has been studied (23, 57). Placement of food into the stomach elicited an increase in celiac artery flow, followed later, by an increase in superior mesenteric artery flow; whereas, the infusion of digested food into the duodenum (bypassing the stomach) resulted in an increase in superior mesenteric artery flow and no change in celiac artery flow (23). Also, luminal placement of digested food in a jejunal segment increased blood flow to this segment but did not alter flow to the

adjacent segment having no contact with food (57). The increased flow was mainly due to an increased flow to the mucosal layer (57). These studies thus suggest that the postprandial hyperemia in the splanchnic viscera is a local phenomenon.

The purpose of the present study was twofold: 1) to further evaluate the hypothesis that the intestinal hyperemia produced by the luminal presence of digested food is a local phenomenon and 2) to examine the effects of the concentration (and/or tonicity) of the food in the lumen and intestinal motility on the local hyperemia.

CHAPTER II

LITERATURE REVIEW

This review of the literature is divided into two sections, the format of each consisting of an historical approach. The first section, entitled Feeding and Circulatory Adjustments, deals with studies performed on unanesthetized subjects. Emphasis is placed on the development of views concerning postprandial circulatory adjustments. This section has two subdivisions: a) "Studies prior to 1966" and b) "Studies after 1966." The second section, entitled Studies on Isolated Intestinal Segments, deals with studies in which blood flow of intestinal segments were measured in anesthetized dogs. Emphasis is placed on the search for the regulatory mechanisms responsible for the postprandial intestinal hyperemia.

Feeding and Circulatory Adjustments

(a) "Studies prior to 1966"

One of the earliest studies relating changes in circulatory hemodynamics with digestion of a meal was that of Collett and Liljestrand in 1924 (24). Using the nitrous oxide equilibrium method they measured the cardiac outputs

of two human subjects after a light meal (bread, butter, cheese, and water) or a heavy meal (smorgasbord, oatmeal and milk, and beef with fried potatoes). The cardiac output increased an average of 1.5-2.5 liters, thirty to sixty minutes after a meal (light or heavy), gradually declining towards fasting levels thereafter. The fasting level was reached three to four hours after a light meal, taking somewhat longer (up to nine hours) after a heavy meal. An increase in heart rate (5-15 beats/minute) was also noted thirty to sixty minutes following a light or heavy meal; and returned to fasting levels three hours after a light meal, but remaining elevated three hours after a heavy meal.

In 1929 Grollman (33) performed a more extensive study on variations in cardiac output of men following meals by using more subjects and also monitoring systemic arterial pressure. Using an acetylene gas method, he noted an increase in the cardiac output after the ingestion of either a light meal (bread, meat and a cup of coffee with sugar and cream) or a heavy meal (bread, meat, sweet chocolate and 150 cc of milk). The cardiac output increased immediately and reached a maximum thirty minutes after the ingestion of a meal. The maximum increases in cardiac output were greater and of longer duration after a heavy meal (1.0-2.0 liter/min and lasting for three hours) than after a light meal (0.5-0.9

liter/min and lasting for one hour). Changes in blood pressure were negligible, whereas, pulse rate increased transiently and returned to fasting levels within one hour. Based on this evidence, Grollman suggested that dilation was occurring in the splanchnic vascular bed with a concommitant increase in cardiac output, thus maintaining systemic pressure virtually unaltered.

In the following years, further studies were carried out using various gas equilibrium methods which substantiated the data generated by Collett and Liljestrand (24) and Grollman (33). In 1931 Starr and Collins (50) using an ethyliodide gas method noted increases in cardiac output of 50 percent and 20 percent in two human subjects after the ingestion of a meal. Then, Gladstone in 1935 (31) used a modified ethylene gas method to measure the cardiac output of human subjects under basal and postprandial conditions. He found that during the digestion of a mixed meal of moderate size, the cardiac output increased by an average of 25 percent (range: 11-47 percent) above basal levels.

Although Grollman (33) had suggested that the splanchnic vasculature exhibited vasodilation postprandially, one of the earliest studies to actually measure changes in splanchnic blood flow during digestion of a meal was performed by Herrick et al. in 1934 (36). They made use of the

thermostromuhr method of Rein to measure flow in a single vessel leaving the liver of a dog (thoracic portion of the posterior vena cava). A meal of milk (250 cc), eggs (2), and glucose (1 gm/kg) produced an average increase in blood flow of about 54 percent, whereas a meal of cooked meat and cereal resulted in a 74 percent increase in blood flow. The maximum increase in blood flow occurred within two to three hours and remained elevated for five to six hours. The same year Herrick et al. (37) using the same method (thermostromuhr) measured flow in the femoral, carotid and superior mesenteric arteries of conscious dogs during digestion of a meal. After the ingestion of a milk-egg-glucose meal or a meal of meat and cereal the superior mesenteric artery blood flow increased within ten minutes, and reached a maximum of 60 percent above fasting levels within ninety minutes. The flows in the femoral and carotid arteries also increased by 60 percent above fasting levels after the ingestion of a milk-egg-glucose mixture. Although they did not measure cardiac output directly they surmised that an increase in cardiac output had occurred. Essex et al. in 1936 (28) also using the thermostromuhr method observed increases in blood flow through the circumflex branch of the left coronary artery in conscious dogs of as much as 84 percent after a meat meal. They suggested that this increase in coronary flow was due to the increased work load of the heart during digestion.

The thermostromuhr method was subjected to severe criticism in the early 1940s (32) forcing investigators to once again use more indirect methods to study circulatory adjustments following meals. Abramson and Fierst in 1941 (1) used the venous occlussion plethysmographic method to follow changes in peripheral blood flow (hand, forearm, and leg) of human subjects after the ingestion of a protein meal (lean meat, cottage cheese, egg white and gelatin) or a carbohydrate meal (vegetables, sweetened stewed and raw fruits, and sweetened fruit juices). The ingestion of a carbohydrate meal produced no significant changes in blood flow to the hand, forearm, or leg. The ingestion of a protein meal produced an increase in blood flow sixty to ninety minutes following the ingestion of the meal, first in the hand, and later, in the forearm and leg. They also noted an increase in pulse rate and pulse pressure after ingestion of either meal, suggesting that an augmentation of cardiac output had occurred.

Berman et al. in 1950 (3) measured changes in cardiac output with a ballistocardiogram and heart rate with an electrocardiogram in humans following the ingestion of a meal (90 gms of carbohydrates, 40 gms of protein, 40 gms of fat). The cardiac output increased by an average 1.4 liters/minute thirty minutes after the meal, representing a 24 percent increase. The electrocardiogram indicated that

the heart rate had increased by an average of five beats/minute thirty minutes after the meal. In the same year, Paine and Shock (42) using an undamped ballistocardiograph noted increases in the cardiac index of humans (cardiac output/body surface area) of 12 percent above the basal level after a meal (33 gms of protein, 110 gms of carbohydrates, 35 gms of fat). This increase persisted for three and one-half hours and did not return to preprandial levels for five to six hours.

Brandt et al. in 1955 (4) by means of the bromsulphalein (BSP) clearance method studied the effect of oral protein and glucose feeding on splanchnic blood flow in humans. The estimated splanchnic blood flow increased by 35 percent within twenty to fifty minutes following the ingestion of a protein meal (250 gms of chopped beef) and decreased by 8 percent following the ingestion of a glucose meal (100 gms of glucose and lemon juice).

Reininger and Sapirstein in 1957 (43) compared the cardiac outputs and estimated blood flows to the major organs of fasted (water only ad libitum) and fed (water and food ad libitum) rats. After an intraperitoneal administration of nembutal the cardiac output was determined by dye dilution with Evans blue dye as the indicator and the fractional distribution of the cardiac output among the organs by extraction ratios of intravenously injected K^{42}. The fasted

rats had an average cardiac output of 172 ± 38 ml/kg/min, while the fed rats had an average cardiac output of 223 ± 59 ml/kg/min. Blood flows to the liver (34%), gut and spleen (32%), myocardium (18%), skin (31%), and kidneys (32%) were all increased in the fed rats suggesting that following meals all organs increased their blood flows by amounts proportional to the increased cardiac output.

Reininger and Nutik in 1960 (44) using the bromsulphalein clearance method studied changes in the cardiac outputs of unanesthetized dogs upon ingestion of a large protein meal (116 gms of liver) or an isocaloric fat meal (73 gms of beef fat). A significant increase in the cardiac output of 23 percent and 34 percent above fasting values were noted one and two hours, respectively, after the liver meal. There were no significant changes found in cardiac output after the fat meal.

Castenfors et al. in 1961 (10) used the BSP clearance method to estimate splanchnic blood flow after the ingestion of 400-500 cc of 20 percent glucose solutions in normal human subjects and in patients who had been subjected to partial gastrectomy. Within twenty minutes after the ingestion of the hypertonic glucose solution, a 25 percent increase in splanchnic blood flow was noted in the normal subjects and a 71 percent increase was noted in the gastrectomized subjects. The pulse rate increased by 94 percent

and 30.3 percent in the normal and gastrectomized subjects, respectively. The systemic pressure was unchanged in the normal subjects, whereas the blood pressure in gastrectomized subjects decreased leading to circulatory collapse.

In 1961 Rushmer et al. (45) using a new method for the monitoring of blood flows through individual arteries obtained results conflicting greatly with the bulk of the existing data. They monitored blood flows through the abdominal aorta, renal artery, superior mesenteric artery and hepatogastric artery of conscious dogs via pulsed ultrasonic flowmeters. Following the consumption of a plate of standard dog food, they noted "a questionable reduction" in flows through the renal artery and abdominal aorta. They found no change in the superior mesenteric artery flow and in only one instance did the flow through the hepatogastric artery increase following a meal. In 1965 Jones et al. (41) also published data that was in contrast to previous studies concerning the effect of feeding on cardiac output. Using indocyanine green dye and a densitometer, they noted that twenty minutes following the ingestion of a meal (30% protein, 30% fat, and 40% carbohydrates), the cardiac index of human subjects was unaltered from the pre-meal values.

Dagenais et al. in 1966 (26) using a dilution technique (with Coomassie blue dye as the indicator) followed changes in the cardiac output of men after the ingestion of

either a carbohydrate-rich meal or a protein-rich meal. An electrocardiograph and sphygmomanometer were used to monitor heart rate and systolic blood pressure respectively. Of twenty-four human subjects, eight received a protein-rich meal (480 gms of filet mignon), eight received a carbohydrate-rich meal (600 gms of apple juice, applesauce, ice cream, butter cake, and maple syrup) and eight fasted throughout the study. The subjects fed a protein meal evidenced increases in cardiac output (46%), heart rate (21%), and systolic pressure (9%). The changes in these parameters were significantly greater than those of the fasting subjects, being maximal at 180-270 minutes after the ingestion of the meal. The subjects fed a carbohydrate-rich meal evidenced increases in cardiac output of 34 percent and in systolic pressure of 9 percent, again, being maximal at 180-270 minutes following the meal. The heart rate also increased 15 percent within ninety minutes, but returned to control levels by 180 minutes. The fasted subjects evidenced an increase in cardiac output of 21 percent being maximal at 180-270 minutes.

In summary, most of the studies performed prior to 1966 indicated that the blood flow to the splanchnic viscera increases postprandially in humans (4, 10), dogs (36, 37), and rats (43). Only one study yielded data suggesting that blood flow to the digestive organs of dogs remains unchanged following a meal (45). A great majority of the investigators

monitoring cardiac output changes occurring after meals noted an average increase in cardiac output of 25-45 percent in humans (3, 24, 26, 31, 33, 42, 50), dogs (44), and rats (43) postprandially, whereas, only one study generated evidence which indicated that the cardiac output was unaltered in humans (41) after a meal. Furthermore, the composition of the meal consumed seemed to affect the extent of the increase in splanchnic blood flow (36, 4), as well as, the degree and duration of the increase in cardiac output (24, 26, 33, 44). Splanchnic blood flow tended to increase to a greater extent after a heavy meal (meat or protein) than after a light meal (glucose or eggs). The cardiac output increased to a greater extent and remained elevated longer after a heavy meal (meat or protein) than after a light meal (glucose or fat). Those studies which measured systemic arterial pressure and heart rate indicated that the systemic pressure either remained unaltered (10, 33) or increased slightly (26), and the heart rate increased twenty to sixty minutes after the ingestion of a meal (24, 33). It was generally assumed that the increase in splanchnic blood flow after meals was a result of an increase in cardiac output. Additional studies which measured regional blood flow postprandially in man, dogs, and rats suggested that the blood flow increased to the extremities (1, 37, 43), heart (28, 43), kidneys (43), and brain (37, 43) in addition

to the splanchnic viscera. Only one study noted "a questionable reduction in renal blood flow"; however, the same study indicated that the blood flow to the digestive organs remained unaltered following a meal (45). Thus, the prevalent concept of cardiovascular adjustments postprandially held that, after meals, there was an augmentation of cardiac output which was shared by all the major organs of the body.

(b) "Studies after 1966"

After 1966 many investigators used various blood flowmeters to study cardiovascular responses to meals in conscious animals. These flowmeters allowed the direct monitoring of blood flow through individual vessels. Burns and Schenk in 1967 and 1969 (7, 8) monitored blood flows through the superior mesenteric artery and the ascending aorta of conscious dogs with implanted electromagnetic blood flow transducers. After the ingestion of a meal (15 ounces of horsemeat) the cardiac output was unaltered (as inferred from the blood flow through the ascending aorta) whereas, the superior mesenteric artery flow began to increase within five minutes after ingestion reaching a plateau fifty minutes later (average peak flows being 71% above fasting levels). In this study, the fasting superior mesenteric artery flow was 7.5 percent of the cardiac output, but it increased to 14.6 percent during digestion.

A more in-depth study of the cardiovascular (systemic and regional) responses to anticipation, ingestion and digestion of food was reported by Fronek and Stahlgren in 1968 (29). The cardiac output and flows through the brachiocephalic, superior mesenteric, and external iliac arteries of conscious dogs were measured with implanted electromagnetic flow transducers. Systemic pressure and heart rate were monitored by a catheter implanted into the descending aorta. Following an eighteen-hour fast, a can of dog food (450 gms) was presented to the animals. During the anticipation period cardiac output, systemic pressure, heart rate and flows through the brachiocephalic and external iliac arteries increased significantly, whereas, superior mesenteric artery flow remained unaltered. During ingestion of the meal, cardiac output, systemic pressure and heart rate continued to rise reaching a maximum during the first minute after starting ingestion. Also, during the first minutes of ingestion, flow in the brachiocephalic artery continued to increase, whereas superior mesenteric artery flow began to increase and external iliac artery flow began to decrease. By one hour after feeding the cardiac output, blood pressure and flows through the brachiocephalic and external iliac arteries had returned to prefeeding levels; heart rate remained slightly elevated and the superior mesenteric artery reached its maximum increase in flow (33%).

By the third hour after ingestion blood pressure, heart rate and cardiac output were at control levels, with superior mesenteric artery flow still 30 percent above control levels, and brachiocephalic and external iliac artery flows decreasing to 80 percent and 75 percent of control levels, respectively. They suggested that the observed changes in the measured hemodynamic variables during the anticipation and ingestion of food could be attributed to a generalized sympathetic response, whereas during digestion a selective increase in flow occurs in the superior mesenteric artery at the expense of the vascular beds supplied by the external iliac and brachiocephalic arteries.

Vatner et al. in 1969 (54) using pulsed ultrasonic or electromagnetic flowmeters placed on the ascending aorta, mesenteric, renal and iliac arteries and blood pressure transducers in the aorta studied the hemodynamic responses to meals in unanesthetized dogs and baboons. They found transient increases in blood pressure, heart rate and cardiac output during the presentation of food, which returned to control levels fifteen minutes after ingestion. Mesenteric flow increased after ingestion (with a 300% increase above fasting levels occurring within one hour) and remained elevated for six hours. Renal artery flow was essentially unchanged, but iliac flow fell as much as 20 percent below fasting levels. The same group (Vatner et al.) in 1970 (55),

placed flowmeters of various types on the ascending aorta and on the cranial mesenteric artery of dogs for the measurement of cardiac output and mesenteric flow respectively prior to and after the ingestion of a variety of meals (meat-flavored dog food, condensed milk, horsemeat and gravy, raw or cooked hamburger, dry dog food and beef fat). Pressure gauges were attached either directly to the aorta or to a femoral cannula for the monitoring of systemic pressure and heart rate. Anticipation and ingestion of the meals resulted in increases in heart rate (79%), cardiac output (63%) and aortic blood pressure (31%), whereas, mesenteric flow transiently decreased (10%). Cardiac output, heart rate and blood pressure returned to control levels after 10-30 minutes, whereas superior mesenteric artery flow had begun to increase. Superior mesenteric artery flow reached a maximum (15%-200% above fasting levels) fifty to sixty minutes after ingestion of food, and then returned gradually to control levels within three to seven hours after ingestion of food. In fasted, muzzled dogs the presentation of food, but not allowing the dogs to eat, also produced an increase in mesenteric resistance on seeing the food and a decrease in resistance fifteen minutes later. The decreased resistance returned to control levels within thirty minutes after the presentation of food. The increase and decrease in mesenteric resistance in these dogs, however,

were less marked than those which occurred when they were allowed to eat and rest after eating. Alpha-adrenergic blockade (phenoxybenzamine, 15 mg/kg, i.v.) or beta-adrenergic blockade (propanolol hydrochloride, 3 mg/kg, i.v.), respectively, reversed or attenuated the circulatory responses during anticipation of food. Neither alpha- nor beta-adrenergic blockade altered the mesenteric vasodilation during digestion. Cholinergic blockade (atropine, 0.1-0.2 mg/kg, i.v.) prevented the postprandial mesenteric vasodilation, whereas, bilateral vagotomy did not.

Vatner et al. in 1970 (56) in an extended study using the same techniques as in earlier studies (54, 55) measured cardiac output, blood pressure, heart rate and flows through the cranial mesenteric artery, left renal artery, left iliac artery and left circumflex coronary artery. During the presentation and ingestion of food, cardiac output (62%), blood pressure (33%), and heart rate (79%) all increased; but, returned to control levels within ten to thirty minutes and remained there up to seven hours postprandially. The mesenteric, iliac and renal vascular beds evidenced similar responses during anticipation, ingestion, and digestion of food as reported earlier by the same author (54, 55). The left circumflex coronary flow increased during the anticipation and ingestion of food, returned to control levels within fifteen to twenty minutes,

and remained at fasting levels throughout the remainder of the study.

In summary, the use of more sophisticated instrumentation and methodology in the studies undertaken after 1966 yielded results which were both supportive and contradictory of earlier studies. The direct measurement of blood flow through the superior mesenteric artery of either dogs (7, 8, 29, 54, 56) or baboons (54) with flowmeters strongly supported the earlier supposition that splanchnic vasodilation occurs postprandially. More specifically, during anticipation and ingestion of food the superior mesenteric artery flow remained unaltered (29) or decreased slightly (55), then began to increase within five to fifteen minutes (7, 29), attained a maximum fifty to sixty minutes after the ingestion of a meal (7, 29, 54, 55), and remained elevated for three to seven hours. In contrast to earlier studies direct measurement of aortic root flow indicated that the cardiac output remains essentially unaltered during digestion of a meal (barring transient increases during anticipation and ingestion of food) (7, 8, 29, 54, 56). The systemic pressure and heart rate followed the same general pattern of changes as did the cardiac output (29, 54-56). Direct measurements of regional blood flow (excluding the splanchnic vascular bed) also yielded results different from those of earlier studies. Blood flow through the renal and coronary

arteries remained unaltered during digestion of a meal (54, 56), whereas, blood flows through the brachiocephalic and external iliac arteries (representing flow through the skin and musculature of the extremities, respectively) tended to decrease (29, 55). Thus, recent evidence suggests that rather than an augmentation of cardiac output resulting in an increase in blood flow to all vascular beds, there is a redistribution of an unchanged cardiac output, postprandially, favoring the splanchnic vascular bed at the expense of blood flow to the extremities. It appears that the transient cardiovascular responses which occur during the anticipation and ingestion of a meal are mediated via the sympathetic nervous system; while those occurring during digestion may be mediated by some cholinergic system other than the vagi (55).

Studies on Isolated Intestinal Segments

Brodie and Vogt in 1910 (5) used the oncometric method (a modification of the plethysmographic method) to study blood flow through an isolated intestinal loop (125 cm long) of chloroform anesthetized dogs prior to and after the intraluminal placement of water and salt solutions. The intraluminal placement of water caused a gradual decrease in flow as was the case when the intestinal segment was empty.

Saline solutions (between 0.9-1.3%) caused a slight increase in flow in two of the three animals. When a 2 percent solution of NaCl was placed in the lumen, a striking increase in blood flow of 200 percent was observed within twelve minutes and remained at that level for one hour. Magnesium sulfate (47%) caused an increase in flow of over 11.2 percent by twenty minutes after placement. The maximum increase in flow observed during any procedure was 1.3 cc/gm/min. The volumes of the test solutions upon removal suggested that water and NaCl were absorbed; whereas, magnesium sulfate caused exsorption of fluid. They concluded that when the intestine was actively involved in absorption or secretion, blood flow to the intestine increased by 39 percent over basal levels. In the same year Brodie et al. (6) using the same method (oncometric) studied blood flow changes in an isolated loop of the intestine of chloroform anesthetized dogs after the intraluminal placement of Witte's peptone (10% in normal saline). The blood flow through the intestinal loop was increased by 66 percent, 57 percent, and 28 percent above control levels eighteen, forty, and sixty minutes after the placement of the peptone solutions.

Fifty years passed during which no studies concerned with gut lumen contents and intestinal blood flow were performed using isolated in situ intestinal segments.

By the late 1950s the growing clinical interest in the "dumping syndrome" necessitated experimental situations which would simulate the clinical manifestations. Thus, Huse and Henshaw in 1960 (40) used electromagnetic flowmeters to study changes in the blood flows through the mesenteric, renal, carotid and femoral arteries of pentabarbital anesthetized dogs after the injection of 50 cc of 50 percent glucose into the proximal jejunum. The mesenteric artery flow increased an average of 45 percent, with maximal increases occurring between twenty and thirty-five minutes after the glucose injection. In contrast, there was an average decrease of 36 percent in carotid flow, 34 percent in renal flow, and 32 percent in femoral flow. Cardiac outputs (determined by a dilutional technique using renografin) decreased by 20 percent. Based on these results they suggested that there was a redistribution of the cardiac output favoring the splanchnic bed at the expense of blood flow to other areas.

In 1967 Swan and Grafe (51) used electromagnetic flowmeters to study changes in blood flow through the superior mesenteric artery upon injection of 150 ml of 50 percent dextrose into the proximal jejunum of pentobarbital anesthetized dogs. The mean mesenteric blood flow increased within minutes after the injection, reaching a value 52 percent above fasting levels by ninety minutes (accompanied

by a fall in mesenteric vascular resistance of 36 percent). The increases in mesenteric flow persisted for 150 minutes.

Other studies were carried out using isolated jejunal segments and different methods of measuring changes in blood flow which, in general, substantiated the data obtained with flowmeters. Varro et al. in 1967 (53) measured venous outflow from an isolated denervated jejunal loop of chloralose anesthetized dogs while introducing isotonic solutions of saline, glucose, or glycine into the lumen. When isotonic glucose was in the lumen the jejunal blood flow increased to 20 percent above the control flow values. The introduction of an isotonic glycine solution resulted in a 55 percent increase in blood flow from the control flow values. The intraluminal injection of isotonic saline produced an increase in intestinal blood flow of 21 percent. The introduction of a comparable amount of air into the jejunal lumen produced no significant change in blood flow. Chou et al. in 1967 (15) measured the changes in venous outflow from isolated naturally perfused in situ jejunal segments of anesthetized dogs following luminal placement of 2.5 percent, 5.0 percent, 20 percent, or 50 percent glucose solutions. Polyethylene glycol (PEG) was used as a control solution. The 20 and 50 percent glucose solutions increased the venous outflow over precontrol levels by 9 and 18 percent, respectively. The 2.5 percent and 5.0

percent glucose solutions, although failing to increase the venous outflow above precontrol levels, did increase the flow over postcontrol levels. Van Heerden et al. in 1968 (52) using the I^{33} clearance technique measured blood flow from an isolated loop of the proximal jejunum of pentobarbital anesthetized dogs while perfusing the lumen with 5 percent or 25 percent glucose solutions at 4 cc/min for one hour. They found no significant increase in blood flow while perfusing the loop with 5 percent glucose, but a 52 percent increase in flow while perfusing with 25 percent glucose. They also used two differently labeled microspheres Sr and Sc (as control and test respectively) to determine the distribution of blood flow in different sections of the intestine during luminal perfusion of a jejunal loop with 25 percent glucose solutions. It was noted that all portions of the intestine possessed similar amounts of radioactivity prior to the glucose perfusion. During the perfusion of the lumen with hypertonic glucose, it was found that the section containing 25 percent glucose possessed 54 percent greater radioactivity than did the nonperfused section.

Since electrolytes are continuously secreted and absorbed by the gastrointestinal tract, the effects of intraluminal placement of salt solutions isosmotic or hypertonic on the local blood flow were assessed. Chou et al. in 1968 (16) studied the effects of intraluminal placement of

isosmotic solutions of NaCl, KCl, $MgCl_2$, and $CaCI_2$, on the venous outflow and the luminal pressures of two naturally perfused *in situ* ileal segments of anesthetized dogs. One segment served as the test segment and contained one of the four isosmotic salt solutions while the other segment served as the control segment and contained an isosmotic polyethylene glycol solution. As compared to the changes occurring in the control segment, the intraluminal placement of the salt solutions produced the following results. The venous outflow was decreased by NaCl and $MgCl_2$ solutions, unchanged by the $CaCl_2$ solution, and increased by the KCl solution. The motility was increased (as inferred from changes in luminal pressure) only by the KCl solution. Dabney *et al*. 1969, (25) using two naturally perfused isolated ileal segments of anesthetized dogs studied the effects on ileal venous outflow of placing hypertonic salt solutions in the lumen. Hypertonic KCl, $MgCl_2$, $CaCl_2$, NaCl, and polyethylene glycol (PEG) solutions (all 1500 mOsm/kg) increased the venous outflow, with hypertonic KCl causing the greatest increase and hypertonic PEG causing the least increase in venous outflow.

Chen *et al*. in 1969 (11) assessed the possibility that the local hyperemia produced by the luminal presence of hyperosmotic salt solutions is mediated by mucosal nerves. They compared the effects of intraluminal placement of NaCl,

KCl, $MgCl_2$, or $CaCl_2$ (all 1500 mOsm/kg) on the luminal pressures, and the volume, osmolarity, and cation concentrations of the venous outflow from two adjacent gut segments of anesthetized dogs. The luminal presence of any of these solutions significantly increased the volume, as well as, the cation concentration of the venous outflow. They repeated the procedure after anesthetizing the mucosa with 0.4 percent dibucaine. After the dibucaine treatment KCl significantly decreased venous outflow, NaCl and $CaCl_2$ failed to increase venous outflow, while $MgCl_2$ increased venous outflow to the same extent as before the dibucaine treatment. The cation concentration following KCl or $MgCl_2$ placement increased to greater levels than observed prior to the dibucaine treatment. The rise in cation concentration with NaCl or $CaCl_2$ in the lumen was the same before and after the dibucaine treatment. The increases in venous osmolarity were the same before and after the treatment for all salt solutions studied. They concluded that the mucosal nerves are partly responsible for the local hyperemia produced by luminal placement of hyperosmotic salt solutions.

Hsieh et al. in 1970 (38) measured the venous outflow and luminal pressure of an in situ duodenal segment of anesthetized dogs while perfusing the lumen with acidified Tyrode's solutions (pH 3.0, pH 2.5, pH 2.0, and pH 1.5) and glucose solutions (5% and 50%) at 4 ml/min for sixteen minutes.

The Tyrode's solutions of pH 2.0 and pH 1.5 increased the venous outflow above the control flow (with Tyrode's pH 7.4 in the lumen) by 10.1 percent and 17.7 percent, respectively. The 50 percent glucose solution increased the venous outflow by 13.1 percent. The duodenal motility was increased by the Tyrode's solution of pH 1.5. The Tyrode's solutions of pH 3.0 and pH 2.5 and the 5 percent glucose solutions did not effect duodenal blood flow. These results were essentially the same as those noted by Chou et al. 1970 (17). Chou et al. 1971 (19) further investigated the effects of lumen pH and osmolarity on duodenal blood flow. The perfusion of Tyrode's solutions of pH 8.0, pH 9.0 or pH 11.0 into the lumen of in situ duodenal segments of anesthetized dogs at 4 cc/min for sixteen minutes failed to change the venous outflow. Perfusion with glucose solutions (1100 and 1500 mOsm/kg) also did not alter the duodenal venous outflow.

Burns et al. in 1971 (9) investigated the role of local nerves in the regulation of local jejunal blood flow and/or motility when 10 ml of hyperosmotic KCl, NaCl (1500 mOsm/kg) or glucose (3000 mOsm/kg) were in the lumen. Isotonic polyethylene glycol was used as the control solution. The intraluminal placement of any of the test solutions (KCl, NaCl, or glucose) resulted in an increase in venous outflow and a decrease in vascular resistance. During the local intra-arterial infusion of tetrodotoxin (a neurotoxin)

the intraluminal placement of KCl increased vascular resistance, NaCl either decreased or did not alter resistance, but glucose still decreased resistance. Tetrodotoxin abolished the increased motility caused by NaCl and glucose and attenuated that caused by KCl. They concluded that vascular and motility responses to lumen hypertonicity are, in part, mediated by intramural nerves.

In 1971, Chou et al. (18) examined some of the possible mechanisms involved in the local intestinal hyperemia produced by the luminal presence of hyperosmotic glucose solutions. Using two adjacent jejunal segments of anesthetized dogs, they compared the effects of intraluminal placement of 2.5, 5.4, 20 and 50 percent glucose solutions and 8.5, 34 and 85 percent polyethylene glycol solutions on the volume, osmolarity, and glucose concentration of the venous outflows and the luminal pressures of the two segments. The intraluminal placement of all the glucose solutions increased the volume and glucose concentration of the venous outflow. The venous osmolarity was increased to the same extent by hypertonic polyethylene glycol solutions as by the hypertonic glucose solutions of the same osmolarity. However, the 34 percent polyethylene glycol solution (osmotically comparable to the 20% glucose solution) did not alter the venous outflow and the 85 percent polyethylene glycol solution (osmotically comparable to the 50% glucose solution)

increased flow to a lesser extent than did the 50 percent glucose solution. All the hypertonic solutions studied increased jejunal motility. Local intra-arterial infusion of 2.5 percent and 5.4 percent glucose solutions increased the venous glucose concentrations to levels comparable to those caused by the intraluminal placement of any glucose solution, but did not alter the venous outflow of the jejunal segments. In the same study they reexamined the local increase in venous outflow produced by the intraluminal placement of 50 percent glucose after exposing the jejunal mucosa to 0.4 percent dibucaine (a local anesthetic). After the dibucaine treatment the increase in flow produced by the 50 percent glucose solution was either abolished or attenuated as was the jejunal motility. They concluded that the increase in flow with hypertonic glucose in the jejunal lumen is a local phenomenon. The local hyperemia is not a result of hyperglycemia, but may be mediated by: 1) local vascular hypertonicity and 2) mechanisms which can be blocked by anesthetizing the mucosa.

Hsieh and Chou in 1972 (39) used a bioassay method to investigate the possible role of humoral substances in the local increase in blood flow and motility when either acid or foodstuff was in the duodenal lumen of anesthetized dogs. The bioassay organ was an isolated segment of jejunum which was pump perfused with duodenal venous blood while

acidified Tyrode's solution (pH 1.5) or a liquid diet food (Sego) was being infused into the duodenal lumen. The results indicated that, while acidified Tyrode's or Sego (diet food mixture) was in the duodenal lumen, the local vascular resistance decreased and its motility increased. Simultaneously, the vascular resistance of the assayed jejunal segment decreased and its motility increased. They concluded that humoral substances which could lower vascular resistance and increase motility appeared in the duodenal venous blood when the lumen contained acid or foodstuff. That same year Chou et al. (20) studied the effects of the local intra-arterial infusion of secretin, cholecystokinin and pentagastrin on the vascular resistances of duodenal and jejunal segments, spleen, whole forelimb, and muscle and skin of the forelimb of anesthetized dogs. Secretin decreased the vascular resistance of all organs studied (-10%) when the local blood concentration of secretin was raised by 0.01 u/ml. Cholecystokinin (CCK) decreased the vascular resistances of the duodenal and jejunal segments (-20%) when the local blood concentration of CCK was raised by 0.05 u/ml. CCK did not alter the vascular resistance of the forelimb, skin, or muscle. Gastrin decreased the vascular resistance of the duodenal and jejunal segments (-14%) when the local blood concentration of gastrin was raised by 0.04 ug/ml. Gastrin had no effect on the splenic resistance. They concluded that

the vasodilator action of secretin is equipotent in the duodenum, jejunum, spleen, skin, and muscle; while that of cholecystokinin is greater in the gut than in the spleen and absent in the forelimb. Gastrin dilates the gut vasculature, but does not alter the splenic vasculature.

In 1973, Chou et al. (22) studied the effects of the hormones secretin, pentagastrin and cholecystokinin on the vascular resistance of the heart and kidney. While the left coronary or renal artery of pentobarbital anesthetized dogs were pump perfused at a constant rate, the hormones were infused at various rates into the local arteries. Secretin decreased the resistance of the coronary (-13%) and renal (-9%) vasculatures when the local blood concentration of secretin was raised by 0.03 u/ml and 0.01 u/ml respectively. These responses were not as great as the response produced by secretin in the duodenal, jejunal, splenic, forelimb, skin and muscle vasculatures studied earlier (21). Increments in the local concentration of cholecystokinin over the ranges 0.006-0.13 u/ml and pentagastrin over the ranges 0.04-0.85 ug/ml did not significantly alter coronary or renal vascular resistance. They concluded that the G.I. hormones exert little or no influence on the vascular resistance of the heart or kidney.

Some of the previous studies using isolated in situ intestinal segments suggested that the increase in flow

produced by the intraluminal presence of foodstuffs, nutrients, or electrolytes was a local phenomenon. Thus, Chou et al. in 1974 (23) studied the time course of the changes in blood flow through the celiac and superior mesenteric arteries in chloralose anesthetized dogs, during the infusion of food into the stomach (200 ml in 3 minutes) or during the infusion of digested food into the duodenum, at 4 cc/min. Introduction of food into the stomach increased the celiac artery blood flow within five minutes and the hyperemia was maintained for thirty minutes, after which, the flow gradually returned to control levels. In contrast, the flow in the superior mesenteric artery (SMA) remained at control levels until thirty minutes after the introduction of food into the stomach, at which time, it increased and remained elevated for at least three hours. The infusion of digested food into the duodenal lumen resulted in an increase in blood flow through the SMA within three minutes after starting the infusion and remained elevated throughout the infusion. The blood flow in the celiac artery was unaltered throughout the infusion period.

In summary, in the early 1900's Brodie and Vogt suggested that when the intestine is actively involved in the process of absorption or secretion its blood flow increases (5). Since then, many studies have suggested that the postprandial increase in blood flow to the gut is a

local phenomenon involving only the portion of the intestine which is in contact with foodstuff (food, glucose, salts, etc.) (15, 16, 18, 23, 25, 52). By the use of isolated in situ intestinal segments investigators attempted to elucidate the possible mechanisms which regulate the local gut blood flow.

The pH of the gut contents appeared to affect its local blood flow. When the pH of a solution (Tyrode's) perfusing the duodenal lumen was lowered below 2.0 the motility and local blood flow of the duodenum was increased (17, 38). When the pH of the same perfusate was raised above 11.0 there was no change in the local blood flow or wall activity of the duodenum (19).

Intraluminal placement of hypo- or isotonic glucose solutions into the jejunal lumen either increased (15, 18, 53) or did not alter the blood flow (52), whereas, perfusion of isotonic glucose through the duodenal lumen did not alter local blood flow (38). The placement of an isotonic glycine solution into the jejunal lumen increased the blood flow (53). Isotonic salt solutions in the jejunal (53) or ileal (16) lumen decreased or did not alter local blood flow, with the exception of potassium salts which increased the flow (16). Hypertonic glucose or salt solutions in the duodenum, jejunum or ileum all increased local blood flow (9, 11, 15, 18, 25, 38, 40, 51, 52). Intraluminal placement of a hypertonic

solution (3000 m0sm/kg) of a nonabsorbable substance, polyethlene glycol into the jejunal lumen also resulted in an increase in local blood flow (18, 25). The hyperemia produced by all the hypertonic solutions was associated with increases in the venous osmolality (11, 18) and in some cases, the motility of the intestinal segments (9, 18). The luminal placement of all absorbable hypertonic solutions (salts and glucose) resulted in elevations of the local blood concentrations of the respective chemicals (11, 18).

The participation of local nerves in the initiation of the local hyperemia produced by the intraluminal presence of hyperosmotic substances was investigated with the use of an anesthetic or a neurotoxin. The application of dibucaine (a local anesthetic) to the mucosal surface abolished or attenuated the increase in blood flow produced by the intraluminal placement of hyperosmotic glucose, KCl, NaCl, or $CaCl_2$ (11, 18), but was ineffective in altering the hyperemia produced by hyperosmotic $MgCl_2$ (11). The treatment with dibucaine also prevented the increase in motility observed with hypertonic glucose in the lumen (18). The increased cation and glucose concentrations of the local venous blood caused by luminal placement of the hyperosmotic salt and glucose solutions were unaltered or increased by the dibucaine treatments (11, 18). The local intra-arterial

infusions of tetrodotoxin (a neurotoxin) abolished the increase in local blood flow produced by the intraluminal placement of hypertonic KCl and NaCl solutions, but did not affect the hyperemia produced by hypertonic glucose (9). Tetrodotoxin also either attenuated or abolished the increase in intestinal motility when the solutions were in the lumen.

The possible implication of gastro-intestinal hormones in the local intestinal hyperemia was established by a bioassay method (39). Local intra-arterial infusions of secretin, cholecystokinin, or pentagastrin produced dilation of duodenal and jejunal vasculatures (20), but had little or no effect on the heart or kidney vasculature (22).

CHAPTER III

METHODS

The purpose of the present study was twofold: 1) to further evaluate the hypothesis that the intestinal hyperemia produced by the presence of digested food is a local phenomenon and 2) to examine the effects of the concentration (and/or tonicity) of the food in the lumen and the intestinal motility on the local hyperemia. To meet this purpose three series of experiments were performed using two different surgical preparations. A total of twenty-four mongrel dogs (10-20 kg in weight), which had been fasted for twenty-four hours were used. The animals were anesthetized by an intravenous administration of either a chloralose-urethane mixture (75 mg chloralose and 500 mg urethane/kg) or sodium pentobarbital (30 mg/kg). They were artifically ventilated with room air via an endotracheal tube with a positive pressure respiration pump (Harvard, Model 607, Dover, Mass.). The systemic arterial pressure was continuously monitored via a cannula in the femoral artery with a pressure transducer (Statham, p23 Gb, Hato Rey, Puerto Rico) and recorded on a direct writing oscillograph (Sanborn, 7700 Series, Waltham, Mass.).

Preparation of the Digested Dog Food Mixtures and Their Supernatants

One can of beef dog food (Alpo, Allen Products Co., Inc., Allentown, Pa.) was emptied into a high-speed blender and vigorously mixed until a homogenous blend was formed. The pH of the homogenate was adjusted to approximately 7.0 (6.8-7.2) with sodium hydroxide. To the blend, 750 mg of pancreatic enzymes (Viokase, Viobin Corp., Monticello, Ill.) were added for the hydrolysis of the major food constituents (protein, starch, and fat). To facilitate the digestion of the food, the mixture was gently stirred on a magnetic stirrer (Arthur H. Thomas, Model 15, Philadelphia, Pa.) for five to six hours at room temperature. From the *in vitro* digested food, four different food mixtures were prepared: undiluted digested food (1:0 Food), 1:2 diluted digested food (1:2 Food), 1:4 diluted digested food (1:4 Food), and 1:9 diluted digested food (1:9 Food). Distilled water was used to dilute the digested food.

Four cans of digested food were homogenized and the homogenate of each can was divided into two halves. One half of the homogenate was used to prepare the four digested food mixtures in the same manner as described above. Samples of the four food mixtures were centrifuged at 19,250 x G, the supernatants removed and their osmolalities determined by the freezing point depression method with an osmometer

(Advanced Instruments, Inc., Model 67-31LAS, Newton Highlands, Mass.). The other half of the homogenate was refrigerated for 24 hours and then treated in the same manner as the first half of the homogenate.

Control Solutions

Isosmotic solutions of polyethylene glycol (PEG; molecular weight 4000) and sodium chloride (normal saline) were used as controls for the food mixtures. Both the control solutions and the food mixtures were kept in a constant temperature water bath (Precision Scientific Co., Chicago, Ill.) at 37°.

Surgical and Experimental Procedures

(A) Preparation I

In sixteen dogs, under chloralose-urethane anesthesia, the abdominal cavity was exposed through a midline incision. The superior mesenteric artery was located and approximately 2-2.5 cm of the artery was dissected free from the adjacent tissue. A noncannulating electromagnetic blood flow transducer (Series 5000, Biotronex Laboratory, Inc., Silver Springs, Md.) was fitted snugly around the artery and grounded to adjacent tissue. For the determination of zero flow, a hydraulic occluder of silastic was placed around the artery distal to the flow transducer. The electromagnetic

flow transducer was attached to a pulsed-logic flowmeter (Biotronex Laboratory, Inc., Silver Springs, Md.). The flowmeter was electronically calibrated with a direct writing oscillograph (Sanborn, 770 Series, Waltham, Mass.) for the continuous recording of blood flow through the superior mesenteric artery. Previous volume calibrations, performed with a beaker and stop watch in vitro (with normal saline) and in vivo (in a few representative animals), had verified the accuracy and linearity of the flow transducers.

The proximal duodenum was located and an L-shaped plastic tube (i.d. = 3.5 mm, o.d. = 6.5 mm) was inserted into the duodenal lumen. The tube was secured in place such that the opened end, inside the duodenum, faced the aboral portion of the small intestine. The tube was used to deliver digested food into the duodenal lumen with a pump (Sigma-motor, Model TM 10, Middleport, NY). Using the natural vascular pattern of the mesentery as a guide, a segment of jejunum about 10-12 cm in length and 30-35 cm aboral to the ligament of Treitz was isolated. A plastic tube (i.d. = 1.1 cm, o.d. = 1.6 cm) was inserted into the cut end of the jejunum proximal to the isolated segment to allow for drainage of the food being pumped through the duodenal-jejunal portion of the intestine (60-70 cm in length).

The isolated in situ jejunal segment had a blood supply which stemmed from a single artery and was drained

by a single vein. After an intravenous administration of an anticoagulant (heparin sodium, 6 mg/kg), the vein draining the segment was exposed and cannulated with polyethylene tubing (i.d. = 1.7 mm, o.d. = 2.4 mm). During the cannulation procedure, care was taken to insure that the artery and nerves were not disturbed. The venous blood draining the segment was collected in a reservoir initially containing 200 ml of 6 percent dextran in normal saline. The blood was continuously returned to the dog from the reservoir with a variable-speed pump (Sigmamotor, Model T6 SH, Middleport, NY) via a cannulated femoral vein at a rate equal to the venous outflow. A rubber tube (i.d. = 3 cm, o.d. = 0.5 cm) was placed into the lumen of the isolated segment for the introduction and withdrawal of fluids. Both ends of the segment were tied and the mesentery cut to exclude collateral blood flow. The naturally perfused in situ jejunal segment, outside the abdominal cavity, was covered with a plastic sheet to maintain a moist environment and kept at 37°C via a heating lamp.

Using the preparation described above the blood flows through the superior mesenteric artery and the isolated jejunal segment were simultaneously measured during two series of experimental maneuvers: 1) luminal perfusion of the duodenal-jejunal portion of the intestine with food

(Series 1) and 2) placement of food into the isolated jejunal segment (Series 2).

Series 1

Ten ml of isosmotic PEG was placed into the isolated jejunal segment. When the blood flow through the superior mesenteric artery and the venous outflow from the jejunal segment became stable, undiluted digested food was pumped into the duodenal lumen at 4 cc/min for one hour. While the food was traversing the duodenal-jejunal portion of the intestine, the isolated jejunal segment retained the isosmotic PEG in its lumen. The blood flow through the superior mesenteric artery was continuously recorded and one-minute samples of the venous outflow from the jejunal segment were collected with a graduated cylinder at 5, 15, 20, 25, 35, 50 and 60 minutes after the start of the perfusion. The volume of blood in the graduate cylinder was recorded and returned to the reservoir after each collection. This procedure was executed in a total of six dogs.

Series 2

Ten ml of isosmotic PEG was placed into the isolated jejunal segment. When the blood flow through the superior mesenteric artery and the venous outflow from the jejunal segment became stable, the PEG solution was withdrawn and 10 ml of undiluted digested food was introduced

into the jejunal lumen. The food remained in the jejunal lumen for fifteen minutes during which, blood flow through the superior mesenteric artery was continuously recorded, and one-minute samples of the venous outflow from the jejunal segment were collected with a graduated cylinder at 6, 9, 12 and 15 minutes following the introduction of the digested food. The volume of blood in the graduate cylinder was recorded and returned to the reservoir after each collection period. This procedure was executed in a total of ten dogs.

(B) Preparation II

In eight dogs, under sodium pentobarbital anesthesia, the abdominal cavity was exposed through a midline incision. A loop of jejunum about 25-30 cm aboral to the ligament of Treitz was exteriorized. The jejunal loop was divided into two segments of equal length such that the blood flow from each segment was drained by a single vein. After an intravenous administration of heparin sodium (6 mg/kg), the vein draining each segment was cannulated with polyethylene tubing (i.d. = 1.7 mm, o.d. = 2.4 mm). Care was taken to insure that the arteries and nerves remained intact. The venous blood draining the two segments was directed into a reservoir initially containing 200 ml of 6 percent dextran in normal saline. The blood was continuously pumped back

from the reservoir to the dogs via a cannulated femoral vein at a rate equal to the total venous outflow. A rubber tube (i.d. = 0.3 cm, o.d. = 0.5 cm) was placed into the lumen of each segment for the introduction and withdrawal of fluids. At all other times the tubes were used for the monitoring of the luminal pressures of the segments. The luminal pressures were measured with pressure transducers (Statham, p23 Gb, Hato Rey, Puerto Rico) and recorded on a direct writing oscillograph (Sanborn, 7700 Series, Waltham, Mass.). Both ends of each segment were tied and the mesentery cut to exclude collateral blood flow. The naturally perfused in situ jejunal segments, outside the abdominal cavity, were covered with a plastic sheet to maintain a moist environment and kept at 37°C via a heating lamp.

Using this double jejunal segment preparation, a series of experiments were done to compare the effects of luminal placement of the four food mixtures (i.e., undiluted food, 1:2, 1:4, or 1:9 diluted food) on the volume and osmolality of the venous outflow, changes in the placed volumes, and luminal pressures of the segments. One of the two segments was used as the experimental segment and the other segment was used as the control segment. Each experiment consisted of three successive fifteen minute periods (precontrol, test, and postcontrol). During the

precontrol and postcontrol periods, 10 ml of normal saline were introduced into the lumen of both segments. During the test period, 10 ml of either undiluted digested food or one of the dilutions of digested food were introduced into the experimental segment and 10 ml of normal saline into the control segment. During each period, four three-minute collections of the venous outflows from both segments were made with three one-minute intervals between them. The venous blood was collected in graduated cylinders and, after its volume had been recorded, returned to the reservoir. The last three-minute flow collections from the experimental segment during the precontrol and test periods were used for the measurement of osmolality. Osmolality was determined by the technique of freezing point depression with an osmometer (Advanced Instruments, Inc., Model 67-31LAS, Newton Highlands, Mass.). After each period, the luminal contents of each segment were removed and the volume measured with a syringe. The lumen of each segment was then gently washed with normal saline.

Using the experimental protocol described above the effects of any three or all four of the digested food mixtures were examined in a random sequence in a given double segment preparation. The two segments were alternately used as experimental and control segments. After each animal had been sacrificed, the two jejunal segments

were dissected clear of mesentery and weighed on a top loading precision balance (Mettler, Model P1200, Hightown, NJ).

Expression of Data and Statistical Methods

The data obtained from the experiments in which blood flows through the superior mesenteric artery and an isolated jejunal segment were simultaneously measured were expressed in percent of control values. Student's t-test modified for paired comparisons (49) was used in the statistical analysis of the results.

In the experiments done with the double jejunal segment preparation, all of the blood flow data were expressed as ml/min/100 grams of the intestinal tissue. The blood flow data of the last three-minute flow collections in each period were considered the most representative of that period and used in the statistical analysis. Resistances were calculated and expressed as mm Hg/ml/min/100 gm of intestinal tissue. The resistance data were tabulated in an identical manner as the blood flow data. The luminal pressure data were separated into two components: 1) basal luminal pressure and 2) phasic luminal pressure. The value of the basal luminal pressure was the average of the lowest point of all the pressure waves occurring during each period.

The value of phasic luminal pressure was the average of the amount of vertical spread of all the pressure waves (i.e., the difference between peak pressure and basal pressure) occurring during each period. The basal and phasic luminal pressures recorded during the last three three-minute flow collections of each period were then averaged and expressed in mm Hg. The blood flow, resistance and pressure values of the first three-minute flow collection period were omitted from tabulation because in some experiments these values were apparently influenced by distention of the lumen after the introduction of fluids. The influence, however, normally lasted only two minutes. Changes in the volume of the placed fluids over a fifteen minute stay in the lumen were obtained by taking the difference between the volume of fluid introduced and removed from the jejunal lumen during each period. All of the data (blood flow, resistance, changes in the volumes of the placed fluids, basal and phasic luminal pressures, and venous osmolality) were compared from one period to the next with Student's t-test modified for paired comparisons (49). Concurrent changes in blood flow and resistance from precontrol to experimental periods in both segments were also calculated as percent changes from precontrol. The changes that occurred in the experimental segment were then compared to the concomitant changes occurring in the

control segment with Student's t-test modified for paired comparisons (49). Furthermore, an analysis of variance, single classification (49), was used to compare the relative effects of the four different food mixtures on blood flow and resistance.

CHAPTER IV

RESULTS

The results of the first and second series of experiments in which blood flows were simultaneously measured through the superior mesenteric artery (SMA) and a segment of the jejunum are shown in Figure 1. In the first series (Top, Figure 1) digested food was perfused through the duodenal-jejunal portion of the intestine while the isolated jejunal segment contained the control PEG solution. In the second series (Bottom, Figure 1) digested food was placed in the isolated jejunal segment while the rest of the small intestine remained intact. The average systemic arterial pressure was not significantly altered throughout either series of experiments.

As shown in the top panel of Figure 1, blood flow through the SMA significantly increased to 113 percent of its control flow within ten minutes after the start of the perfusion. By twenty minutes after the start of the perfusion, SMA flow increased to 123 percent of control and was maintained at this level for the remainder of the hour.

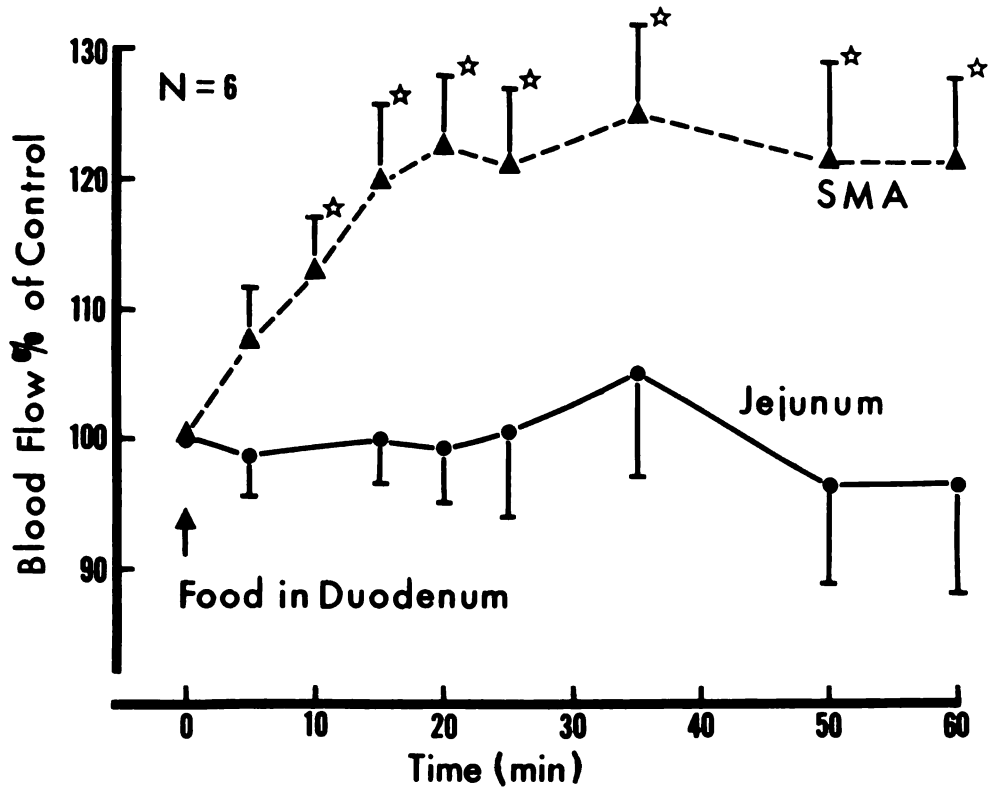
FIGURE 1

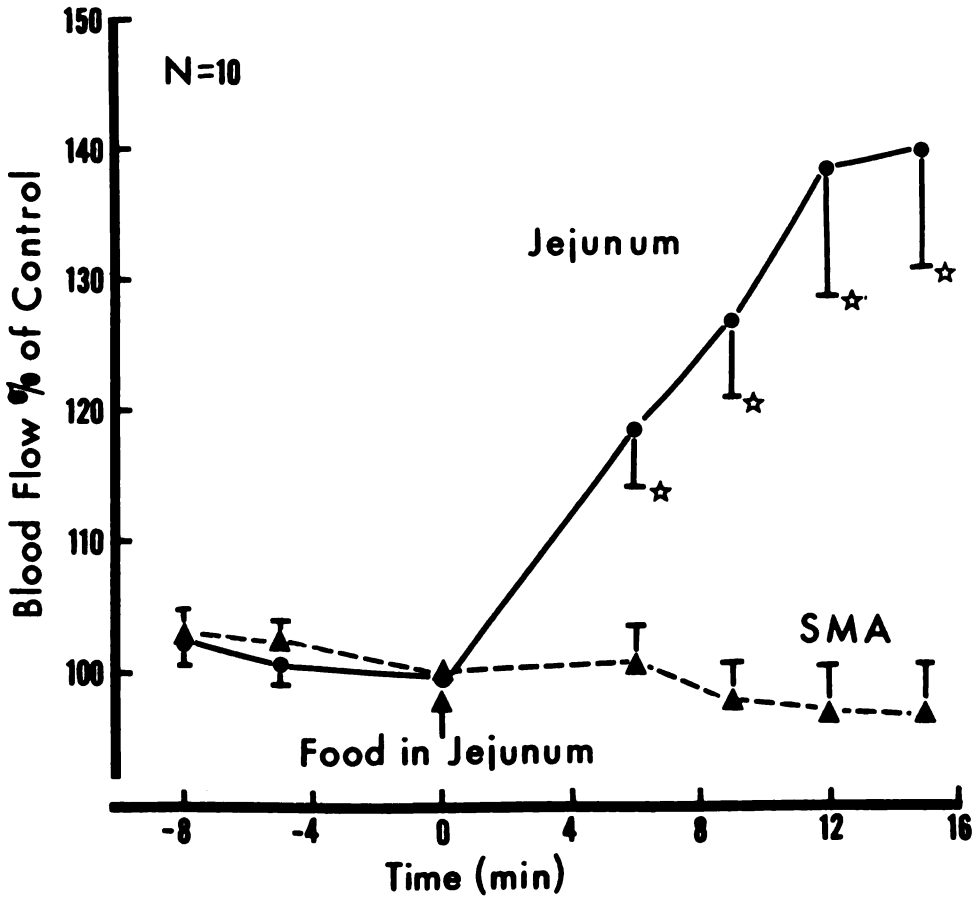
TOP: Blood flow, as percent of control, of the superior mesenteric artery (SMA) and the isolated jejunal segment during infusion of digested food into the duodenum at 4 cc/min. The control flow in SMA = 258 $\pm$ 21 ml/min; the control flow in the isolated jejunal segment = 0.06 $\pm$ 0.05 ml/min/gm (mean $\pm$ S.E.) (N = 6).

*Denotes that the value is statistically different from control at $p < 0.05$.

BOTTOM: Blood flow, as percent of the control, of the superior mesenteric artery (SMA) and the isolated jejunal segment prior to and after luminal placement of digested food into the jejunal segment. The control flow in the SMA = 227 $\pm$ 19 ml/min; the control flow in the isolated jejunal segment = 0.45 $\pm$ 0.03 ml/min/gm (mean $\pm$ S.E.) (N = 10).

*Denotes that the value is statistically different from controls at $p < 0.05$.


N = 6
SMA
Jejunum
Food in Duodenum
Blood Flow % of Control
130
120
110
100
90
0
10
20
30
40
50
60
Time (min)


N=10
Jejunum
SMA
Food in Jejunum
Blood Flow % of Control
150
140
130
120
110
100
-8
-4
0
4
8
12
16
Time (min)

The venous outflow from the isolated jejunal segment, which had no contact with food, did not significantly change from its control value throughout the perfusion period. The average systemic arterial pressure was 126 mm Hg.

The luminal placement of undiluted digested food into the isolated jejunal segment, on the other hand, increased the venous outflow of this segment but did not alter SMA flow (Bottom, Figure 1). The venous outflow from the isolated jejunal segment significantly increased to 119 percent of its control value by the sixth minute, and reached a maximum, 140 percent of control, at fifteen minutes after the intraluminal placement of food. The average systemic arterial pressure was 128 mm Hg.

The results of the experiments performed on the double segment preparation are shown in Tables 1-5. Tables 1 and 2 show the effects of intraluminal placement of one of the four digested food preparations (1:0, 1:2, 1:4, or 1:9 Food) in one segment and normal saline in the other segment on the venous outflows (Table 1) and calculated vascular resistances (Table 2) of the two segments. The luminal placement of undiluted food (1:0 Food), 1:2 Food or 1:4 Food increased the venous outflow and decreased the vascular resistance of the segment containing food (Tables 1 and 2). The venous outflow and vascular resistance of the control segments containing normal saline were not

Table 1. Average venous outflow (ml/min/100 gm) before, during and after luminal placement of undiluted (1:0) or diluted (1:2, 1:4, or 1:9) digested food in one and normal saline (I-NaCl) in the other segment of the double segment preparation.

	Experimental Segment					Control Segment				
	Luminal Contents	Time (min) after placement of fluids			D†	Luminal Contents	Time (min) after placement of fluids			D†
		4-7	8-11	12-15			4-7	8-11	12-15	
1:0 Food (N=6)										
	I-NaCl	46.4	46.4	47.4		I-NaCl	54.5	54.0	55.1	
	1:0 Food	61.6	63.8	65.6	18.2±4.7*	I-NaCl	49.6	51.5	51.8	3.2±1.4
	I-NaCl	46.5	46.9	47.7	17.8±4.0*	I-NaCl	49.1	53.5	59.1	7.2±3.3
1:2 Food (N=7)										
	I-NaCl	55.3	55.7	57.0		I-NaCl	54.0	52.5	51.7	
	1:2 Food	58.9	64.4	66.5	9.5±2.5*	I-NaCl	44.0	44.8	47.1	4.6±2.8
	I-NaCl	49.9	51.0	52.9	13.6±4.2*	I-NaCl	43.8	44.3	46.3	0.8±2.0
1:4 Food (N=7)										
	I-NaCl	40.7	38.3	39.4		I-NaCl	46.1	40.2	41.2	
	1:4 Food	44.3	44.3	48.3	8.9±2.0*	I-NaCl	41.7	39.6	40.9	0.5±2.2
	I-NaCl	40.2	38.3	40.3	8.0±2.6*	I-NaCl	36.0	35.5	37.1	3.8±1.7
1:9 Food (N=7)										
	I-NaCl	52.7	54.3	55.3		I-NaCl	58.9	60.1	59.2	
	1:9 Food	55.3	57.8	59.0	3.6±3.0	I-NaCl	51.8	54.0	54.3	4.9±2.0
	I-NaCl	48.3	51.7	54.4	4.6±2.6	I-NaCl	47.3	49.5	52.6	1.7±2.5

†D = the difference between the last flow values (12-15 min) of two successive periods (ml/min/100 gm ± S.E.).

* Values are statistically significant at $P < 0.05$.

Table 2. Average vascular resistance (mm Hg/ml/min/100 gm) before, during and after luminal placement of undiluted (1:0) or diluted (1:2, 1:4, or 1:9) digested food in one and normal saline (I-NaCl) in the other segment of the double segment preparation.

	Experimental Segment					Control Segment				
	Luminal Contents	Time (min) after placement of fluids			D†	Luminal Contents	Time (min) after placement of fluids			D†
		4-7	8-11	12-15			4-7	8-11	12-15	
1:0 Food (N=6)										
	I-NaCl	3.34	3.23	3.21	0.8±0.2*	I-NaCl	2.83	2.85	2.86	0.3±0.2
	1:0 Food	2.50	2.47	2.38	1.0±0.3*	I-NaCl	3.19	3.12	3.11	0.2±0.1
	I-NaCl	3.42	3.36	3.33		I-NaCl	3.39	3.07	2.93	
1:2 Food (N=7)										
	I-NaCl	2.76	2.78	2.73	0.5±0.1*	I-NaCl	2.71	2.84	2.88	0.2±0.1
	1:2 Food	2.45	2.27	2.20	0.6±0.3	I-NaCl	3.25	3.27	3.11	0.0±0.2
	I-NaCl	3.02	2.89	2.81		I-NaCl	3.26	3.22	3.09	
1:4 Food (N=7)										
	I-NaCl	3.92	4.17	3.83	0.7±0.2*	I-NaCl	3.53	3.84	3.57	0.1±0.1
	1:4 Food	3.33	3.34	3.11	0.4±0.3	I-NaCl	3.68	3.87	3.70	0.2±0.2
	I-NaCl	3.67	3.79	3.52		I-NaCl	4.20	4.23	3.93	
1:9 Food (N=7)										
	I-NaCl	2.66	2.58	2.55	0.2±0.1	I-NaCl	2.81	2.71	2.77	0.3±0.1
	1:9 Food	2.53	2.34	2.32	0.3±0.2	I-NaCl	3.31	3.03	3.04	0.2±0.2
	I-NaCl	2.91	2.75	2.64		I-NaCl	3.60	3.39	3.20	

†D = the difference between the last resistance values (12-15 min) of two successive periods (mm Hg/ml/min/100 gm ± S.E.).

* Values are statistically significant at $P < 0.05$.

significantly altered from control values when food was in the experimental segments (Tables 1 and 2).

The luminal presence of 1:9 Food increased the average venous outflow and decreased the average vascular resistance of the jejunal segment (Tables 1 and 2). These changes, however, were not statistically significant. In five of the seven animals the luminal placement of 1:9 Food increased the flow and decreased the resistance, but in the other two animals there was a decrease in flow and an increase in resistance. Since these changes in the latter two dogs were associated with a decrease in systemic arterial pressure, the increased resistance may be due to an increase in sympathetic activity as a result of the decrease in the systemic pressure. This is supported by the finding that the flow and resistance of the control segment in these two animals also decreased and increased, respectively. In the other five animals the flow and resistance of the control segment or the systemic pressure did not significantly change. The average flow and resistance of the control segment in all these seven animals did not significantly change from one period to the next (Tables 1 and 2).

Table 3 shows the percent change in blood flow and vascular resistance from the precontrol value while one of the four food mixtures was in one segment and normal saline

in the other segment of the double segment preparation. Only the 1:9 Food in the lumen did not significantly alter jejunal blood flow and resistance when the values obtained during the test period were compared to the precontrol values. Since both segments were subjected to the same systemic influences (i.e., blood pressure, systemic nerve activity, etc.) at a given time, any difference in the vascular responses of the two segments can be reasonably attributed to the differences in their luminal contents (21). The changes that occurred from the precontrol to the test periods in the experimental segment were, therefore, compared to those occurring in the control segment (last column, Table 3). This comparison shows that the luminal placement of any of the four digested food mixtures, including the 1:9 Food, significantly increased the venous outflow and decreased the vascular resistance. The data of the last column of Table 3 were also analyzed by an analysis of variance (single classification) to see if the four food mixtures used in this study produced different effects. The analysis showed that their effects on flow and resistance were not statistically different from one another at a p value less than 0.05.

Table 4 shows the mean basal and phasic luminal pressures of the jejunal segments while either normal saline or any of the digested food mixtures was in the lumen. The presence of undiluted food in the lumen increased the mean

Table 3. Percent change from precontrol value of blood flow (Flow) and vascular resistance (Res.) while one of the four digested food mixtures was in the lumen of the experimental segment (E) and normal saline in the control segment (C) (Mean ± S.E.).

Food Mixture (Food:H_2O)	(N)		Experimental Segment (E)	Control Segment (C)	D† = E-C
1:0 Food	(6)	Flow	+39.35±11.75*	-6.71±3.26	+46.06±11.50*
		Res.	-26.93± 4.92*	+6.80±4.21	-33.73± 5.76*
1:2 Food	(7)	Flow	+19.58± 6.08*	-8.55±4.24	+28.14± 5.86*
		Res.	-17.75± 2.96*	+7.51±4.25	-25.26± 4.93*
1:4 Food	(7)	Flow	+24.73± 7.03*	+1.21±5.43	+23.52± 4.35*
		Res.	-17.01± 2.92*	+3.74±3.70	-20.75± 3.07*
1:9 Food	(7)	Flow	+ 7.40± 5.29	-9.15±2.86*	+16.55± 6.17*
		Res.	- 6.90± 3.41	+9.62±4.17	-16.52± 6.06*

†D = difference in changes between the two segments.

* Denotes that the values are statistically significant at $P < 0.05$.

basal luminal pressure of the jejunal segment. The mean phasic luminal pressure was also increased when undiluted food was in the lumen. The increase in phasic pressure, however, was not statistically significant. In five of the six animals the phasic luminal pressure was increased, whereas, in the other animal it was slightly decreased. The luminal placement of 1:2, 1:4, or 1:9 Food did not change the mean basal or phasic luminal pressure of the jejunal segment from those observed during either control period. The mean basal and phasic luminal pressures of the control segments containing normal saline did not change throughout the three periods.

Table 5 shows the effects of luminal placement of any of the four digested food mixtures or normal saline on the venous osmolality and changes in the volumes of the placed substances. In either segment the volume of normal saline in the lumen tended to decrease (ranges: 0.3 ml-1.7 ml) over a fifteen minute period. In contrast, undiluted food increased its volume by an average of 2.5 ml over a fifteen minute stay in the lumen. The undiluted food also significantly increased the venous osmolality by an average of 10.6 mOsm/kg above the precontrol value. The 1:2 and 1:4 diluted foods lost their volume while in the lumen, but these losses were not different from those observed while normal saline was in the lumen. While the

Table 4. Basal and phasic luminal pressures (mm Hg) of two jejunal segments while one of the digested food mixtures or normal saline (I-NaCl) was in the lumen (Mean ± S.E.).

Food Mixtures (Food:H_2O)	(N)	Pressure	Experimental Segment Luminal Contents			Control Segment Luminal Contents		
			I-NaCl	Food	I-NaCl	I-NaCl	I-NaCl	I-NaCl
1:0 Food	(6)	Basal	4.1±0.7	9.7±1.6*	4.6±0.7*	3.2±0.6	3.3±0.5	3.6±0.2
		Phasic	2.5±0.5	11.4±4.8	0.5±0.3	2.4±0.9	2.4±1.7	3.6±2.7
1:2 Food	(7)	Basal	3.4±0.2	3.6±0.5	3.3±0.4	4.0±0.5	3.2±0.6	3.3±0.6
		Phasic	4.7±2.4	4.8±2.4	2.3±1.1	6.3±4.2	4.7±2.0	2.4±0.9
1:4 Food	(7)	Basal	8.1±3.1	8.7±3.5	7.9±2.4	8.1±2.6	8.5±2.5	7.5±2.7
		Phasic	2.4±1.6	1.8±1.8	2.0±1.2	3.8±1.5	3.3±1.3	2.5±0.9
1:9 Food	(7)	Basal	7.3±1.8	5.6±1.3	6.5±2.1	7.8±3.6	7.0±2.9	7.6±3.2
		Phasic	4.4±1.5	4.6±1.9	2.8±1.0	4.0±1.5	4.8±1.9	3.2±1.8

* Denotes that the value is significantly different from the preceding value at $P < 0.05$.

1:9 diluted food was in the lumen it lost a greater amount of volume than did normal saline. The luminal presence of 1:2, 1:4, or 1:9 Food did not significantly change the venous osmolality observed while normal saline was in the lumen.

Table 6 shows the osmolalities of the supernatants of centrifuged undiluted or diluted digested foods. The osmolality of a supernatant obtained from a food mixture prepared from any one can of dog food progressively decreased with each greater dilution. In four of ten cases a supernatant could not be obtained from the undiluted digested food mixture after centrifugation.

Table 5. The osmolality of the venous outflow (Osm., mOsm/kg) and gains (+) or losses (-) in the placed volume (Vol., ml.) while either one of the digested food mixtures or normal saline (I-NaCl) was in the lumen for a 15 minute period (Mean ± S.E.).

Food Mixtures (Food:H_2O)	(N)		Experimental Segment Luminal Contents			Control Segment Luminal Contents		
			I-NaCl	Food	I-NaCl	I-NaCl	Food	I-NaCl
1:0	(6)	Vol.	-0.5±0.7	+2.5±0.8*	-0.7±1.0*	-1.2±0.3	-1.6±0.7	-1.6±1.0
		Osm.	284.3±3.5	294.9±4.0*				
1:2	(7)	Vol.	-1.4±0.6	-0.7±0.6	-0.9±0.4	-1.1±0.6	-1.3±0.6	-1.7±0.5
		Osm.	291.5±3.5	294.5±2.6				
1:4	(7)	Vol.	-0.6±0.4	-1.1±0.5	-0.6±0.4	-0.4±0.3	-0.3±0.4	-0.4±0.2
		Osm.	292.0±2.8	292.1±3.0				
1:9	(7)	Vol.	-1.7±0.6	-3.5±0.8*	-1.1±0.5*	-1.6±0.9	-1.2±0.8	-1.2±1.0
		Osm.	283.4±5.0	282.7±4.4				

* Denotes that the value is significantly different from the value of the preceding period at $P < 0.05$.

Table 6. The osmolalities (mOsm/kg) of supernatants of centrifuged (19,250 x G) undiluted or diluted (1:2, 1:4 or 1:9 with distilled water) digested food.*

Cans of Food	Undiluted Food	Diluted Food (Food:H_2O)		
		1:2	1:4	1:9
1^A	1170	368	302	140
1^B	830	236	126	53
2^A	735	232	133	83
2^B	958	277	166	78
3^A		305	164	93
3^B	1300	365	225	122
4^A	1714	564	316	195
4^B		412	246	136
5		267	173	89
5		280	175	94
Mean ± S.E.	1117.8 ± 146.8	330.6 ± 32.1	202.6 ± 21.2	108.3 ± 12.9

*Supernatants from cans 1-4 bearing superscripts "A" were digested and centrifuged the day the cans were opened. The supernatants bearing superscripts "B" were refrigerated 24 hours prior to digestion and centrifugation. Supernatants from can 5 were digested and centrifuged simultaneously.

CHAPTER V

DISCUSSION

The blood flow through the superior mesenteric artery increases (7, 8, 29, 30, 37, 54-56) and the resistance of this vascular bed decreases (29, 30, 54-56) after a meal in unanesthetized dogs. The increased superior mesenteric artery blood flow during digestion and absorption of a meal has been proposed to be a result of a redistribution of the cardiac output at the expense of blood flow to the extremeties (29, 30, 54-56). Furthermore, the studies performed on anesthetized dogs suggest that the postprandial intestinal hyperemia is not generalized, but is localized only to that portion of the intestine directly in contact with food or glucose (15, 21, 23, 52, 57). The present study was designed to further evaluate the supposition that the intestinal hyperemia due to the luminal presence of food is a local phenomenon. The present study also assessed whether or not and to what degree the local hyperemia could be influenced by the concentration and/or osmolality of the food and intestinal motility. To accomplish these aims two different surgical preparations of the canine small intestine were used.

In one preparation blood flows through the superior mesenteric artery and an isolated jejunal segment were simultaneously measured. Two series of experiments were performed with this preparation. In one series the lumen of the duodenal-jejunal portion of the small intestine (60-70 cm in length) was perfused with digested food, while the isolated segment (10-12 cm in length and immediately distal to the perfused site) was not allowed to have contact with food. In another series digested food was placed in the lumen of the isolated segment while the duodenal-jejunal portion of the small intestine was left intact.

In the second preparation the venous outflows from two isolated adjacent jejunal segments (10-12 cm in length) were simultaneously measured while one segment contained one of the four different concentrations of digested food and the other segment contained normal saline. The osmolality of the venous outflow, changes in the volumes of the luminally placed food, and basal and phasic luminal pressures of the segments were also measured.

As shown in the top panel of Figure 1, perfusion of the duodenal-jejunal portion of the small intestine with food increased the blood flow through the superior mesenteric artery (SMA), but did not significantly alter the flow through the isolated segment having no contact with the food. On the other hand, as shown in the bottom panel of Figure 1,

the placement of digested food into the lumen of the isolated segment increased the flow through this segment, but did not significantly alter the flow through the SMA. Since the isolated segment was perfused by the SMA, the increased flow through this segment should have been accompanied by a simultaneous increase in flow through the SMA as measured with the electromagnetic flowmeter. The absence of a significant change in SMA flow is most probably due to the sensitivity of the flowmeter. The maximum increase in the venous outflow from the isolated segment ranged from 1.6 to 10.3 ml/min, which would represent an increase in SMA flow of 1 to 5 percent above the control level. Since a 5-10 percent experimental error is involved in measuring flow with an electromagnetic flowmeter, a change of this magnitude in SMA flow may not have been detected by the flowmeter. Furthermore, had this change been detected by the flowmeter, a change in flow of 1-10 ml/min would have represented a barely noticeable change of 0.1 to 1 mm in the recorded tracings.

Since the systemic arterial pressure remained unaltered throughout both series of experiments, the increase in blood flow through the SMA or the isolated segment was due to a decrease in their respective vascular resistances. These two series of experiments indicate that the postprandial intestinal hyperemia is a local phenomenon occurring

only in the area exposed to chyme. This supposition is further supported by the results obtained from the experiments performed on the double segment preparation. Luminal placement of undiluted, 1:2 or 1:4 diluted digested food into one of the two segments increased the flow and decreased the vascular resistance of that segment, but did not alter the flow and vascular resistance of the adjacent segment containing normal saline (Tables 1 and 2). These studies thus confirm previous reports which suggested that the postprandial intestinal hyperemia is localized to that section of the small intestine in contact with food (23, 57).

The peak increases in SMA blood flow observed in this study ranged from 20 to 47 percent above the control and occurred fifteen to thirty-five minutes after the start of intraduodenal perfusion with digested food. The magnitude of the increased flows are comparable to those found by other investigators using flowmeters to measure SMA flow in conscious dogs after oral feeding. The mean peak increases in SMA flow during digestion of a meal were found to be 28 percent (30), 33 percent (29), 71 percent (7, 8), and 132 percent (54-56) above prefeeding levels and occurred fifty to sixty minutes after the ingestion of a meal. The peak flow, however, appeared earlier in the present study than in the studies on conscious dogs. This difference is probably due

to the direct infusion of digested food into the small intestine in the present study as compared to the oral ingestion of food in the other studies. When food is ingested orally, the rate of entrance of the food into the small intestine is regulated by the rate of gastric emptying. In chloralose-urethane anesthetized dogs, Chou et al. (23) noted a maximum increase in SMA flow of 52 percent at sixty minutes after the start of the infusion of digested food into the duodenum at 4 cc/min. As compared to their study, the appearance of peak SMA flow is sooner and its magnitude is less in the present study. The reason for these differences is unclear for the surgical preparation and experimental protocol were similar.

The effect of luminal placement of food on compartmental blood flow of the jejunal wall has been studied by Yu et al. (57). They used the radioactive microsphere method to measure blood flow to three adjacent jejunal segments. One segment was left intact and the other two segments contained either undiluted digested food or isotonic PEG. Total wall blood flow to the segment containing food was increased by 47.5 percent as compared to the flow to the segment containing PEG. This is in close agreement with the 46 percent increase in flow to the segment containing food as compared to the flow to the control segment noted in the present study (Table 3, last column). Furthermore, in the

study by Yu et al., the increased jejunal blood flow was due primarily to an increase in flow to the mucosal layer. Since the hyperemia occurred in the mucosal layer, which is in direct contact with food and performs digestive and absorptive functions, their study offers further support to the hypothesis that the postprandial intestinal hyperemia is a local phenomenon.

The second aim of the present study was to examine whether or not and how much the concentration and/or tonicity of food affect the magnitude of the local postprandial intestinal hyperemia. The double segment preparation was used for this study. The concentration of the digested food was altered by adding two, four, or nine parts of distilled water to one part of the digested food. Since the osmolality of these food mixtures is difficult to determine directly by the freezing point depression technique, the food mixtures were centrifuged and the osmolalities of the supernatants were measured. As shown in Table 6, the osmolalities of the supernatants of the digested foods decreased with each greater dilution. The data presented in Table 6 suggest that undiluted food is hypertonic (ranging from 700-1700 m0sm/kg), the 1:2 diluted food is near isotonic (with 8 of 10 values ranging from 230-370 m0sm/kg), the 1:4 diluted food is hypotonic (ranging from 125-320 m0sm/kg with 9 of 10 values below 300 m0sm/kg) and the 1:9

diluted food is even more hypotonic (ranging from 50-200 m0sm/kg with 9 of 10 values being below 140 m0sm/kg). For any given food mixture there was some variation in the osmolality values of the supernatants from one can to the next. This variability is probably due to a variation in the salt, as well as, the water content among different cans of the commercial dog food. In fact, in some cases, after centrifugation of samples of undiluted digested food an aqueous layer was not present in sufficient amounts to obtain a supernatant. In addition, refrigeration (24 hours) of the homogenized dog food prior to digestion and preparation of the food mixtures had varied effects on the osmolalities of the supernatants. As mentioned previously (Chapter II, Methods and Procedures) four cans of dog food were homogenized and the homogenate of each can was divided into two halves. One half was digested and centrifuged that day; and the other half was refrigerated for twenty-four hours, and digested and centrifuged the following day. As shown in Table 6, in half of the cases the osmolalities of the supernatants were lower after refrigeration (cans 1 and 4) and in the other half of the cases the osmolalities were greater after refrigeration (cans 2 and 3). This variability must be largely due to the experimental error involved in dividing the homogenate into two halves. Indeed, if two samples were obtained from one can (can 5, Table 6) and treated

simultaneously the osmolality values of the two samples were similar. It appears, therefore, that the osmolality of these digested food mixtures can not be accurately determined *in vitro*.

The osmolality might change in the lumen as a result of further digestion of the food mixtures in the lumen, probably at the brush border of the mucosal cells. Thus, the apparent osmolality of these food mixtures in the lumen were estimated from changes in the volume placed in the lumen and the local venous osmolality. Chou *et al.* (21) have quantitatively examined the effects of luminal placement of glucose or polyethylene glycol solutions of known osmolality (150-3000 mOsm/kg) on the local venous osmolality and net transmucosal movement of fluid. Hypertonic solutions having osmolalities of 1,200 and 3,000 mOsm/kg increased the venous osmolality by about 11.5 and 15.8 mOsm/kg and increased the lumen volume by about 3.3 and 7.7 ml, respectively. Isotonic solutions having an osmolality of 300 mOsm/kg did not alter the venous osmolality and decreased the lumen volume by about 1.0 ml. Hypotonic solutions having osmolalities of 150 mOsm/kg did not alter the venous osmolality and decreased the lumen volume by about 4 ml. Since the osmolalities of these solutions can be accurately determined by an osmometer and the solutions are not digested in the intestinal lumen, the quantitative changes in venous osmolality

and lumen volume observed in that study can be used as a reference for the osmolality of the digested food in the lumen in this present study.

As shown in Table 5, the luminal placement of undiluted digested food increased the local venous osmolality by 10.6 mOsm/kg and the volume of the placed food by 2.5 ml. These changes are qualitatively similar to those observed while a hypertonic solution of glucose or PEG of 1200 mOsm/kg was in the lumen (21). The osmolality of the undiluted digested food in the lumen therefore, is near 1200 mOsm/kg. This value agrees fairly well with the osmolality of the supernatant of the undiluted digested food (1100 mOsm/kg). The luminal placement of 1:2 and 1:4 diluted food did not alter the venous osmolality and decreased the volume of the placed food by 0.7 and 1.1 ml, respectively. Also, the loss in volume of the placed 1:2 or 1:4 diluted food was not significantly different from the loss in volume of the placed normal saline (1.0). The magnitude of the changes in lumen volume are also quantitatively similar to those observed while an isotonic solution of PEG (300 mOsm/kg) was in the lumen (21). These comparisons indicate that, in the lumen, the osmolality of the 1:2 or 1:4 diluted food is near isotonic. As shown in Table 6, the osmolality of the supernatant of 1:2 Food is near 300 mOsm/kg, but that of 1:4 Food is much lower than 300 mOsm/kg. In addition to the

previously discussed experimental error which may be involved in the determination of the osmolality in vitro, intraluminal digestion of the food mixture might also contribute to the increased osmolality of 1:4 diluted food in the lumen. The luminal placement of 1:9 diluted food did not alter the venous osmolality and decreased the volume of the placed food by 3.5 ml. The loss in lumen volume observed while 1:9 diluted food was in the lumen is greater than the loss in volume of the placed normal saline. Thus the 1:9 diluted food is probably hypotonic in the lumen. The osmolality of the supernatant of 1:9 diluted food determined in vitro also indicates that this food mixture is hypotonic. Physiologically, the chyme entering the jejunum is nearly isotonic. The food mixtures used in this study clearly included the physiological range of the concentrations and/or tonicity of the chyme entering the proximal jejunum.

As can be seen in Tables 1 and 2, the luminal placement of undiluted food, 1:2 diluted food, or 1:4 diluted food increased the venous outflow and decreased the vascular resistance of the jejunal segments. The luminal placement of 1:9 diluted food did not significantly alter the flow or resistance. The lack of significant changes in flow and resistance in the case of the 1:9 diluted food is probably due to an increase in sympathetic stimulation as a result

of a decrease in systemic arterial pressure in two of the seven animals. In these two animals the venous outflow decreased and the vascular resistance increased. In the other five animals the systemic pressure was not altered and the luminal presence of 1:9 Food increased the venous outflow and decreased the vascular resistance. Table 3 further shows that, as compared to the changes in flow and resistance occurring in the control segments, the luminal placement of any of the four food mixtures, including the 1:9 diluted food, significantly increased the flow and decreased the resistance of the segment containing food. A statistical analysis using a single classification analysis of variance indicated that the magnitude of the increased flow and decreased resistance produced by the luminal placement of any of the four food mixtures were similar. Therefore, it appears that the concentration and/or tonicity of the food, over the range used in this study, is not an important contributing factor in the observed postprandial intestinal hyperemia. Additional support for this conclusion is offered by a comparison of the vascular effects of undiluted digested food and a hypertonic nonabsorbable substance. As described above, the luminal placement of undiluted food increased the venous osmolality by 10.6 mOsm/kg and the lumen volume by 2.5 ml (Table 5). These changes are comparable to the 10.7 mOsm/kg increase in the venous

osmolality and 3.0 ml increase in lumen volume observed when 34 percent PEG solution (1200 mOsm/kg) was in the lumen (21). The osmolality of the undiluted digested food in the lumen, therefore, seems to be near that of the 34 percent PEG solution. While the undiluted digested food increased the jejunal venous outflow by 39 percent above the control level, the 34 percent nonabsorbable PEG solution did not alter the venous outflow. From this comparison, it appears that the hypertonicity of the undiluted digested food in the lumen is not an important factor in the resultant local hyperemia.

In a previous study, Chou et al. (21) have evaluated the role played by the tonicity of the lumen contents in the intestinal hyperemia. Using a double segment preparation, they found that the venous outflows from the two segments were increased to the same extent by the luminal placement of isotonic glucose in one segment and hypotonic glucose in the other segment. In the same study, they compared the venous outflows from the two segments while one contained solutions of hypertonic glucose and the other contained solutions of polyethylene glycol (PEG) of the same osmolality (20% glucose = 34% PEG and 50% glucose = 85% PEG). The luminal placement of hypertonic glucose or PEG of the same osmolality increased the venous osmolality and the lumen volume to the same extent. However, while 20 percent and

50 percent glucose solutions increased the venous outflow, the 34 percent PEG solution did not effect the venous outflow and the 85 percent PEG solution did not increase the venous outflow to the same extent as did the 50 percent glucose solution. Polyethylene glycol is a nonabsorbable, inert substance (48) and does not appear to be vasoactive (11). Thus, they concluded that in addition to a direct vascular effect of hypertonicity some other mechanisms are involved in the increase in intestinal blood flow which occurs while hypertonic glucose is in the lumen.

The contractile state of the intestinal wall can influence intestinal blood blow (2, 13, 14, 27, 34, 35, 46, 47). Elevations in intraluminal pressure or strong tonic contractions of the intestine compress the intramural vessels and decrease intestinal blood flow (2, 27, 34, 35, 47). On the other hand the blood flow through the intestine is augmented by rhythmic contractions or decreases in wall tension of the gut via a pumping action or an increase in vascular transmural pressure, respectively (14, 34, 46, 47). As shown in Table 4, only the luminal presence of undiluted digested food in a jejunal segment increased the basal and, in most cases, the phasic luminal pressures of that segment. The basal luminal pressure is an indication of the intestinal tonus or tonic contractions while the phasic luminal pressure is an indication of rhythmic contractions.

Sidky and Bean (47) have indicated that the two types of intestinal contractions (tonic and rhythmic) exert opposite effects on the local intestinal blood flow. Since both the basal and phasic pressures were increased by the undiluted digested food in the present study, the effect of the former may have nullified the effect of the latter on the venous outflow from the jejunal segment. Thus, to what extent the increased motility of the jejunal segment contributed to the local hyperemia caused by the luminal presence of undiluted digested food is difficult to evaluate. However, Chou et al. (21) have also noted that an increase in motility of a jejunal segment during the luminal presence of a hypertonic glucose solution was not strong enough to alter the venous outflow from that segment. Furthermore, all of the three diluted food mixtures increased the venous outflow to an extent similar to that of undiluted food, but did not significantly alter the basal or phasic luminal pressures. Thus, it appears that the jejunal motor activity does not play a major role in the local hyperemia when food is in the lumen.

CHAPTER VI

SUMMARY AND CONCLUSIONS

The blood flow through the superior mesenteric artery increases postprandially. This hyperemia has been suggested to be localized to that portion of the intestine directly in contact with food. In the present study two different surgical preparations of the canine small intestine were used to evaluate the hypothesis that the intestinal hyperemia is a local phenomenon. In addition, the influences of the concentration and/or tonicity of the digested food and intestinal motility on the local hyperemia were examined.

In one preparation the blood flows through the superior mesenteric artery (SMA) and an isolated jejunal segment were simultaneously measured while digested food was pumped into the duodenal lumen or placed into the isolated jejunal segment. In the former experiment the isolated segment was not allowed to have contact with food; while in the latter experiment the duodenal-jejunal portion of the intestine was left intact. In the other preparation the venous outflows and luminal pressures (basal and phasic) of two isolated <u>in situ</u> jejunal segments were simultaneously

measured while one segment contained one of the four different concentrations of digested food and the adjacent segment contained normal saline. The four food mixtures were: undiluted digested food, and digested food diluted 1:2, 1:4, and 1:9 with distilled water. As an indicator of the osmolality of the digested food in the lumen the osmolality of the venous outflow and changes in the volume of the placed food or normal saline were also measured. Furthermore, the four digested food mixtures were centrifuged and the osmolalities of the supernatants were determined *in vitro*.

The results of these studies are summarized as follows:

1) The following results were obtained from the study done with the preparation in which the blood flows through the SMA and an isolated jejunal segment were simultaneously measured.

   a) Perfusion of the duodenal-jejunal portion of the small intestine with food increased the SMA blood flow, but did not alter the flow through the isolated jejunal segment.

   b) Placement of food into the isolated jejunal segment increased the flow through that segment, but did not significantly alter the flow through the SMA.

2) The following results were obtained from the study done with the preparation in which the venous outflows from two isolated jejunal segments were simultaneously measured.

   a) Luminal placement of undiluted digested food, 1:2 or 1:4 diluted digested food in one segment significantly increased the flow and decreased the vascular resistance of that segment without affecting the flow or resistance of the adjacent segment which contained normal saline.

   b) Intraluminal placement of undiluted or any of the diluted digested food mixtures increased the venous outflow and decreased the vascular resistance of the jejunal segment as compared to the concomitant changes in flow and resistance occurring in the adjacent segment containing normal saline.

   c) The magnitude of the mean percent peak increase in flow or decrease in vascular resistance produced by all four food mixtures were statistically similar.

   d) The undiluted digested food increased its volume over a fifteen minute stay in the lumen.

Normal saline, 1:2 or 1:4 diluted food lost similar amounts of their volume while in the lumen. The 1:9 diluted food lost a greater amount of volume than did normal saline.

e) Only the luminal placement of undiluted digested food increased the local venous osmolality, the basal luminal pressure, and the phasic luminal pressure.

3) The osmolalities of the supernatants of centrifuged undiluted, 1:2 diluted, 1:4 diluted, and 1:9 diluted digested foods in vitro were approximately 1100, 331, 203, and 108 mOsm/kg, respectively.

The following conclusions are drawn from these studies:

1) The increase in intestinal blood flow during the intraluminal presence of digested food is, indeed, a local phenomenon.

2) In vitro, undiluted food is hypertonic, 1:2 diluted food is nearly isotonic, and 1:4 and 1:9 diluted foods are hypotonic.

3) In the lumen, undiluted food is hypertonic, 1:2 and 1:4 diluted foods are nearly isotonic, and 1:9 diluted food is hypotonic.

4) The local hyperemia produced by the presence of digested food in the lumen of the jejunum is not affected by the concentration and/or tonicity of the food or the motor activity of the jejunal wall.

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