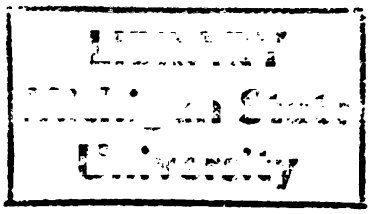


This is to certify that the

dissertation entitled

Contributions of Endogenous Prostaglandins to the Postprandial Intestinal Hyperemia

presented by

Martin John Mangino

has been accepted towards fulfillment
of the requirements for

Ph.D. degree in Philosophy

Major professor

Date July 23, 1985

CONTRIBUTIONS OF ENDOGENOUS PROSTAGLANDINS TO THE POSTPRANDIAL INTESTINAL HYPEREMIA

By

MARTIN JOHN MANGINO

A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Physiology

1985

ABSTRACT

CONTRIBUTIONS OF ENDOGENOUS PROSTAGLANDINS
TO THE POSTPRANDIAL INTESTINAL HYPEREMIA

By

Martin John Mangino

The postprandial intestinal hyperemia is characterized by an increase in blood flow and metabolism in those portions of the intestine exposed to chyme. This response is complex with many factors involved such as hormones, oxidative metabolism, histamine and prostaglandins. Many prostaglandins are synthesized in the intestine, and inhibition of prostaglandin synthesis has been shown to potentiate food-induced increases in intestinal blood flow and oxygen uptake. The purpose of this study was to elucidate more closely the role of endogenous prostaglandins in the vascular response to intestinal nutrient absorption. Therefore, the effects of intraluminal placement of food on jejunal blood flow were studied before and during infusions of arachidonic acid, a prostaglandin precursor, and selective inhibitors of thromboxane synthesis.

A dose-response series of experiments indicates that intra-arterial infusions of arachidonic acid elicits a biphasic effect on jejunal vascular resistance. At low doses, arachidonic acid increased jejunal vascular resistance while at higher doses it decreased vascular

resistance. The increase in jejunal vascular resistance associated with low doses of arachidonic acid was abolished when the animals were pretreated with aspirin 48 hours prior to the experiment and all effects of arachidonic acid on jejunal vascular resistance were abolished with mefenamic acid.

Placement of a digested food solution into the jejunum significantly increased local blood flow and oxygen uptake. Arachidonic acid infused intravenously, intra-arterially or placed into the lumen with the food solution significantly attenuated the hyperemia associated with food placement. The food-induced increases in oxygen uptake were also attenuated with luminal placement of arachidonic acid. These effects were abolished with pretreatment with the cyclooxygenase inhibitor, mefenamic acid.

The selective thromboxane synthesis inhibitors, imidazole and Sodium 5- (3'-Pyridinylmethyl) Benzofuran - 2 - Carboxylate (U-63557A), had no effect on the postprandial intestinal hyperemia but significantly potentiated the food-induced increases in oxygen uptake. Furthermore, both imidazole and U-63557A had no effect on jejunal glucose absorption.

When digested food was placed into the jejunal lumen, capillary exchange capacity, as indexed by the capillary filtration coefficient, significantly increased over the 16

minute placement period, and imidazole enhanced these effects. Mefenamic acid, however, had no effect on intestinal capillary exchange capacity either before or during food placement.

This study indicates that endogenous intestinal prostaglandins may serve to limit the postprandial intestinal hyperemia. Furthermore, endogenous intestinal thromboxanes appear to be involved in the food-induced increases in oxygen uptake as well as the regulation of intestinal capillary exchange capacity.

To my loving wife Janice
and our little Buddy

ACKNOWLEDGEMENTS

I would like to acknowledge the advice, support, and scientific expertise of my mentor, Dr. C.C. Chou, and the other members of my guidance committee, Dr's. Sparks, Krier, Pittman, and Roth. Also, special thanks to Denise Ingold-Wilcox for her friendship and technical expertise, my parents and family for their undying love and support, and my brother, Dr. Michael Mangino, for the life long encouragement and education.

TABLE OF CONTENTS

	Page
LIST OF TABLES.	v
LIST OF FIGURES	vi-viii
INTRODUCTION.	1
LITERATURE REVIEW	2-30
MATERIALS AND METHODS	31-53
RESULTS	54-95
DISCUSSION.	96-112
CONCLUSIONS	113-115
BIBLIOGRAPHY.	116-130

LIST OF TABLES

Table Page

1. The effects of intra-arterial infusions of arachidonic acid (AA) on the postprandial intestinal hyperemia. Blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P < 0.05$ relative to the corresponding value before infusion, n=7. 61

2. The effects of intravenous infusions of arachindonic acid (AA) on the postprandial intestinal hyperemia. Blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P < 0.05$ relative to the corresponding value before infusion, n=7. 63

3. The effects of intra-arterial infusions of arachidonic acid on the food-induced increases in intestinal blood flow and oxygen uptake after pretreatment with mefenamic acid. $\dot{V}O_2$= oxygen uptake, $\dot{V}O_2$ and blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P<0.05$, n=7. . . . 75

4. The effects of intravenous infusions of U-63557A on the food-induced increases in intestinal blood flow and oxygen uptake ($\dot{V}O_2$). Values expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$. * $P<0.05$, 1 = $P<0.05$ relative to the corresponding value before U-63557A, n=5. 85

5. The effects of imidazole ($5\ mg \cdot min^{-1}$, i.a.) and U-63557A ($5\ mg \cdot kg^{-1}$, i.v.) on jejunal glucose absorption in 7 and 5 dogs, respectively. Values are mean $\pm$ standard error and expressed as $mg \cdot min^{-1} \cdot 100g^{-1}$ 89

LIST OF FIGURES

Figure Page

1. Biosynthetic pathway of the major bisenoic prostaglandins and thromboxanes. 15

2. Schematic representation of the preparation used in most experiments. 34

3. Polygraph chart recording showing the effect of a single bolus of arachidonic acid (300 $\mu g \cdot kg^{-1}$) given into the pulmonary artery on aortic pressure. This was done before and 120 min after i.v. infusions of mefenamic acid (10 $mg \cdot kg^{-1}$). 39

4. Mean venous outflows from 2 adjacent jejunal segments containing normal (NS), NS plus arachidonic acid (AA), food, or food plus AA. Values shown below or above 2 adjacent bars indicate percent differences in flow between 2 bars. * $P < 0.05$ relative to preceding value. ** $P < 0.05$ between 2 values denoted by dotted line. n = 12 43

5. Original polygraph chart recording of the data used to estimate jejunal capillary filtration coefficient (CFC). Solid line (intestinal weight panel) represents the rate of tissue water accumulation following the blood volume shift used in estimating CFC. . . . 49

6. Correlation between changes in venous pressure and changes in capillary pressure in isolated jejunal segments. Dotted line represents the observed regression line of the data, solid line represents 70% transmission of the imposed venous pressure elevations to the exchange vessels. 52

7. Effects of intra-arterial infusion of arachidonic acid on jejunal vascular resistance. Dotted lines indicate a zone of 95% confidence. n = 47 from 7 dogs. AA, arachidonic acid. 56

8. Effects of intra-arterial infusions of various doses of arachidonic acid on jejunal vascular resistance before and after mefenamic acid (10 mg/kg, i.v.) in dogs pretreated with a single oral dose of aspirin (25 mg·kg^{-1}) 48 h before the experiment. The dashed line represents the effects of arachidonic acid on jejunal vascular resistance before mefenamic acid (triangles are actual data points) and the solid line indicates the effects of arachidonic acid on jejunal vascular resistance after mefenamic acid (circles are actual data points). The regression coefficients are significantly different at $P < 0.05$, n = 51 from 6 dogs, AA = arachidonic acid. 59

9. Mean O_2 uptakes from 2 adjacent jejunal segments containing normal saline (NS), NS plus arachidonic acid (AA), food, or food plus AA. Values shown below or above 2 adjacent bars indicate percent differences in O_2 uptake between 2 bars. * $P < 0.05$ relative to preceding value. ** $P < 0.05$ between 2 values denoted by dotted line. n = 5. $\dot{V}O_2$ = O_2 uptake. . . . 68

10. Correlation between changes in food-induced increases in jejunal O_2 uptake and blood flow. Closed circles, food alone; open circles, food plus arachidonic acid (AA). 70

11. Relation between jejunal blood flow and O_2 uptake. Blood flow was altered mechanically. Numbers in parentheses indicate number of measurements. Resting flow before mechanical alterations was 40.2 ± 0.5 ml·min^{-1}·100g^{-1}. 72

12. Vascular response to luminal placement of food before and during intra-arterial infusions of imidazole. Flow values are means ± SEM in ml·min^{-1}·100g^{-1}. n = 14, NS, Normal saline, F, food, $P < 0.05$ relative to before infusion. 78

13. Effect of intra-arterial infusions of imidazole on the food-induced increases in oxygen uptake. $\dot{V}O_2$, oxygen uptake, NS, normal saline, F, food. * $P < 0.05$ relative to NS, ** $P < 0.05$ relative to the corresponding value before imidazole, n = 14. . .. 80

14. Correlation between percent changes in $\dot{V}O_2$ (oxygen uptake) and blood flow elicited by luminal placement of digested food before and during intra-arterial infusions of imidazole. * $P < 0.05$ relative to control. 83

15. Time course of changes in jejunal CFC during luminal placement of food before and during i.a. infusions of imidazole. CFC expressed as $ml \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot 100g^{-1}$. NS = normal saline, F = food. Squares = $P < 0.05$ relative to NS before food, * $P < 0.05$ relative to the corresponding value before imidazole, n = 7. . . . 91

16. Time course of changes in jejunal CFC during luminal placement of food before and after i.v. infusions of mefenamic acid. CFC expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$. NS = normal saline, F = food. * $P < 0.05$ relative to NS, n = 7. 94

INTRODUCTION

The increase in intestinal blood flow associated with nutrient absorption occurs only in those areas of the intestine that are exposed to chyme (34, 36, 87). Furthermore, the stimulus for the postprandial intestinal hyperemia has been shown to be the products of food digestion (37, 125). The mechanisms contributing to this response appear to be multifactorial and complex.

Recently, evidence has been presented that implicate a role for prostaglandins. Prostaglandins are synthesized by all layers of the small intestine (1, 15, 25, 55, 85, 91, 92, 93, 126) and have been shown to be released during the movement of ingestia through the gastro-intestinal tract (45). Furthermore, inhibition of prostaglandin synthesis with indomethacin or mefenamic acid significantly potentiate the food-induced increases in intestinal blood flow and oxygen uptake (63).

The purpose of this study was to examine the effects of the bisenoic prostaglandin precursor, arachidonic acid, on the food-induced increases in intestinal blood flow and oxygenation. Also, in an attempt to determine which prostaglandins may be involved, the effects of selective inhibition of thromboxane synthesis on the postprandial intestinal hyperemia was determined.

LITERATURE REVIEW

Postprandial Intestinal Hyperemia

In 1910, Brodie et al. (27) documented the first evidence of a postprandial hyperemia in the canine small intestine by using a plethymograph method. In 1934, Herrick et al. (77) utilized the thermostromuhr method to measure blood flow in various arteries of the conscious dog. Blood flow through the carotid, coronary, and superior mesenteric arteries increase shortly after a fat, carbohydrate, and protein meal and the increase lasted from 2-5 h. This study indicated that the increase in flow to the small intestine during digestion was not obtained at the expense of blood flow to other organs. These findings were further substantiated by studies conducted between 1940 and 1966. These investigators reported that heart rate, blood pressure, and cardiac output (41, 114) as well as blood flow to almost all organs of the body increased after a meal (114). The flow to various organs of the body was measured by the ^{42}K fractional distribution technique in both fed and unfed rats (114).

More recent studies, however, have yielded different results. The cardiovascular system appears to respond to feeding in two distinctly different phases, i.e., anticipation-ingestion and digestion. During anticipation and ingestion of food, there is an increase in cardiac

output, heart rate, and aortic pressure (61, 131, 133). Mesenteric vascular resistance either increases (131, 133), or does not change (61). Renal resistance increases (131, 133), coronary resistance falls (131, 133), and the vascular resistance of the limbs either increases (61) or decreases (61, 131, 133). These changes that occur during the ingestion phase appear to result from activation of the sympathetic nervous system and can be attenuated or modified by adrenergic blocking agents (132).

The cardiovascular responses to anticipation and ingestion of a meal are brief. Within 5-30 minutes after a meal, cardiac output, heart rate, aortic pressure, and coronary and renal blood flows return to control levels, whereas blood flow through the superior mesenteric artery and pancreas starts to rise and reaches a maximum in 30-90 minutes in the conscious dog (23, 30, 61, 64, 131, 133). The postprandial hyperemia through the superior mesenteric artery lasts for 4-7h and blood flow to the limbs and skeletal muscle decreases (61, 131, 133) or does not change (64). This indicates that a redistribution of the cardiac output in favor of the superior mesenteric artery occurs.

The earlier studies conducted between 1910 and 1966 indicated that feeding results in increases in cardiac output and blood flow through most of the body organs and tissues. More recent studies, however, have more carefully characterized the cardiovascular responses to feeding into

two distinctly different phases. The difference in the findings may be due to basic differences in techniques and equipment used to measure cardiac output and regional blood flow.

The postprandial hyperemia is localized to that portion of the gastrointestinal tract that is exposed to chyme. In 1976, Chou et al. (36) found that placement of a food solution in the stomach of anesthetized dogs resulted in a rapid increase in blood flow through the celiac artery lasting less than one hour. Blood flow through the superior mesenteric artery increased 30 minutes after the intragastric placement of food and remained elevated for over three hours. When they infused food directly into the duodenum, celiac artery flow did not change but superior mesenteric artery blood flow increased and remained elevated for several hours.

The celiac artery perfuses the stomach, pancreas, liver, spleen and proximal duodenum. The authors concluded that the increase in celiac artery blood flow during intragastric placement of food was due to increases in gastric blood flow since it did not occur when food was infused directly into the duodenum. Furthermore, the delay in onset of the increase in blood flow through the superior mesenteric artery was believed to be due to the time required for gastric emptying and the sufficient accumulation of chyme in the duodenum. This study also found that when the venous outflows of two isolated jejunal

segments were measured simultaneously, only the segment exposed to chyme exhibited a hyperemia and this was not sufficient to cause a measurable increase in superior mesenteric artery blood flow. These findings have also been supported by other studies (34, 37, 87).

Gallavan et al. (64) studied the effects of feeding on regional blood flow in the conscious dog using radiolabled microspheres. They found that 30 minutes following ingestion of a meal, the postprandial hyperemia was limited to the duodenum and proximal jejunum and extended to the entire small intestine 90 minutes after feeding. The authors suggested that this may be due to the time required for the movement of chyme along the length of the small intestine.

The postprandial intestinal hyperemia is confined to the mucosal-submucosal layer of the gut wall with no significant change in flow to the muscularis (36, 64, 141). Chou and co-workers have shown this to occur in isolated jejunal segments of anesthetized dogs (36, 64) as well as in the conscious dog (64). They employed the radiolabeled microsphere technique in determining compartmental blood flow within the wall of the small intestine. Bond et al. found that blood flow to all three layers of the small intestine increase uniformly after feeding in the conscious dog (23). Likewise, Bohlen (21, 22) has shown a uniform increase in intestinal vascular diameter in all three layers of the rat small intestine when the lumen is exposed

to a glucose solution. Since the submucosal-mucosal layer receives over eighty percent of the total intestinal blood flow, the contribution of the muscularis layer to the postprandial intestinal hyperemia appears to be minimal.

Chyme that enters the jejunum has various properties that may contribute to intestinal hyperemia and many of these properties have been investigated. Jejunal chyme consists, to a certain extent, of bulk and roughage capable of causing mechanical stimulation. Biber et al. (16) have shown that mechanical stimulation of the mucosa of an isolated jejunal segment, by sliding a vinyl tube over the mucosal surface, increases local blood flow. Another study, however, has shown that luminal placement of undigested food has no effect whereas digested food (consisting of comparable roughage and bulk) increases blood flow to isolated jejunal segments (37). It seems that mechanical stimulation of the mucosal surface by the propulsion and mixing of intestinal chyme is not a normal physiological factor in the popstprandial intestinal hyperemia.

Chyme consists of digested food, undigested food, pancreatic secretions and gallbladder bile. Of these, only digested food illicits an intestinal hyperemia (37). Studies by Siragar and Chou (125) determined the relative contribution of digested fat, protein, and carbohydrate to the intestinal hyperemia in isolated jejunal segments of the dog. They found that fat produces the greatest

hyperemia on a weight basis but protein and carbohydrate also produced increases in flow. Furthermore, all three solutions produced increases in intestinal oxygen uptake. The authors concluded that the intestinal hyperemia probably results from a synergistic effect of all three dietary components.

Although bile itself is not vasoactive when placed into the jejunal lumen, it markedly potentiates the postprandial intestinal hyperemia (37). Kvietys et al. (87) examined the effects of various test meals on jejunal blood flow with and without addition of bile. The authors concluded that bile plays an important role in the postprandial intestinal hyperemia because it potentiates the glucose-induced hyperemia and only in its presence can oleic acid, amino acids, caproic acid, and digested triolein increase intestinal blood flow. The mechanisms of bile-induced potentiation of the postprandial jejunal hyperemia have not been elucidated to date. Bile increases blood flow in the ileum and this may be due to the active absorption of bile salts (38).

The pH of chyme changes drastically from acidic to alkaline during gastric emptying. Intestinal chyme has a pH range of 3.5-7.4 (24, 59). But, intraduodenal perfusion of Tyrode's solutions having pH values between 2.5 and 11 does not alter local intestinal blood flow (35, 80).

Therefore, it seems that changes in the pH of luminal contents associated with gastric emptying does not play a direct role in the postprandial intestinal hyperemia.

The dumping syndrome is a pathological condition characterized by a large increase in blood flow to the liver and upper intestinal tract. These symptoms have been associated with the rapid arrival of hypertonic solutions into the jejunum. It seems at least possible, therefore, that lumen osmolality may play a role in the postprandial intestinal hyperemia. Indeed, it has been shown that placement of solutions having osmolalities above 1500 mOsm/kg increase local blood flow (34). But since lumen contents after a meal have osmolalities betwen 220-320 mOsm/kg (59), it seems unlikely that lumen osmolality plays a role in food-induced increases in intestinal blood flow under normal physiological conditions.

The small intestine is richly inervated from both extrinisic and intrinsic nerves. The role of nerves in the postprandial intestinal hyperemia has been examined in many different preparations (22, 34, 52, 53, 89, 109, 128, 131). In the anesthetized cat, vagotomy has been shown to reduce the hyperemia associated with the placement of fat in the duodenum (53). On the other hand, vagotomy has been shown to have no effect on the postprandial intestinal hyperemia in dogs (128, 131). Blockade of the muscarinic receptors with atropine also seems to generate conflicting results. In the intact gastroinestinal tract of cats (52) and dogs

(131), atropine has been shown to block the nutrient-induced increase in blood flow through the superior mesenteric artery. Atropine, however, had no effect on the hypermia produced in vascularly isolated intestinal preparations of the dog (89, 108) and rat (21, 22). These differences may be due to the relative importance of gastrointestinal motility in intact versus isolated intestinal preparations. Atropine decreases gastrointestinal motility and may decrease the absorptive surface area in contact with chyme. This would be a factor in intact gastrointestinal preparations but of little importance in isolated systems.

The enteric nervous system is located within the wall of the intestine and has been shown to play a role in motility (66) and the hyperemia induced by mechanically stroking the intestinal mucosa (17). A possible role of the enteric nervous system in the postprandial intestinal hyperemia was examined by Nyhof and Chou (109). They reported that methysergide (5-HT blocker), hexamethonium (ganglion blocker) and tetrodotoxin (N_a channel blocker) all failed to alter the vascular or metabolic response to placement of glucose or oleic acid in the jejunum of anesthetized dogs. The increases in blood flow and oxygen uptake produced by glucose or oleic acid, however, were blocked or attenuated after exposing the jejunal mucosa to dibucane, a local anesthetic. Furthermore, dibucane decreased active glucose transport across rat intestinal

sacs and decreased oxygen consumption of canine jejunal mucosa *in vitro*. The authors concluded that nutrient-induced hyperemia appears not to be neurally mediated but may be influenced by neurally mediated alterations in parenchymal metabolism and glucose absorption.

Decentralization of isolated intestinal segments in the dog has been shown to have no effect on the postprandial intestinal hyperemia (108). Furthermore, alpha or beta adrenergic blockade does not influence food-induced hyperemia in dogs (131). Thus, it seems that the role of nerves in the postprandial intestinal hyperemia is very minor at best.

Approximately 13 hormones and paracrine substances have been identified in the gastrointestinal tract, many of which are extremely vasoactive. A recent review by Chou *et al.* (38) looked at the effects of gastrointestinal hormones on intestinal blood flow. The authors concluded that only the vasodilator effect of CCK in the duodenum and jejunum and that of neurotensin in the ileum could be considered physiological since only these two hormones elicited vasodilatation at plasma concentrations observed following a meal. It should also be noted that some hormones such as VIP, substance-P, and enkephalin may act as neurotransmitters or local tissue hormones exerting paracrine effects rather than acting as circulating

hormones. Currently, no evidence is available to verify this possibility as a contributer to the postprandial intestinal hyperemia.

Recently, histamine has been shown to be involved in the postprandial intestinal hyperemia. Chou and Siregar (39) have reported that histamine H-1 receptor blockade significantly attenuates both the vascular and metabolic response to nutrient absorption in isolated canine jejunal preparations. This effect appears to be due only to the H-1 receptor since H-2 receptor blockade with metiamide has no effect on the food-induced increases in intestinal blood flow and oxygen uptake.

Prostaglandins have also been implicated in the postprandial intestinal hyperemia. Gallavan and Chou (63) have shown that inhibition of prostaglandin synthesis with either mefenamic acid or indomethacin significantly potentiates food-induced increases in both intestinal blood flow and oxygen uptake in the canine jejunum. Furthermore, changes in intestinal blood flow and oxygen uptake were significantly correlated both before and after prostaglandin synthesis inhibition. The same correlations have also been observed both before and after histamine H-1 receptor blockade (39). The authors concluded that endogenous prostaglandins serve to limit the postprandial intestinal hyperemia, and this may be due to changes in intestinal oxidative metabolism.

Based on the literature characterizing the postprandial intestinal hyperemia and the possible mechanisms involved, it seems clear that this physiological phenomenon is extremely complex and the mechanisms are multifactorial. An intricate network of physiological feedback loops is beginning to emerge in which prostaglandins appear to play a significant role.

Prostanoids

The prostaglandin story began in 1930 when Kurzrok and Lieb (86) noticed that fresh human semen caused rhythmic contractions and relaxations of human myometrial strips. In 1935 Goldblatt and VonEuler (49, 67, 135) confirmed these observations and believed the active compound(s) originated from the prostate gland and thus coined the term "prostaglandin". In 1959, Eliasson (48) found that VonEuler's "prostaglandin" actually originated from the seminal vesicles which still today remain a major laboratory machine for the production of the cyclooxygenase enzyme system. It wasn't until 1960, however, that Bergstrom and Sjovall (13, 14) determined that prostaglandin was a mixture of biologically active compounds by finally isolating and crystalizing prostaglandin E_1 and prostaglandin $F_{1\alpha}$. Studies by Samuelsson (11) and VanDorp (129) in 1964 determined that prostaglandins are derived from the transformation of fatty acids, especially arachidonic acid which is predominantly

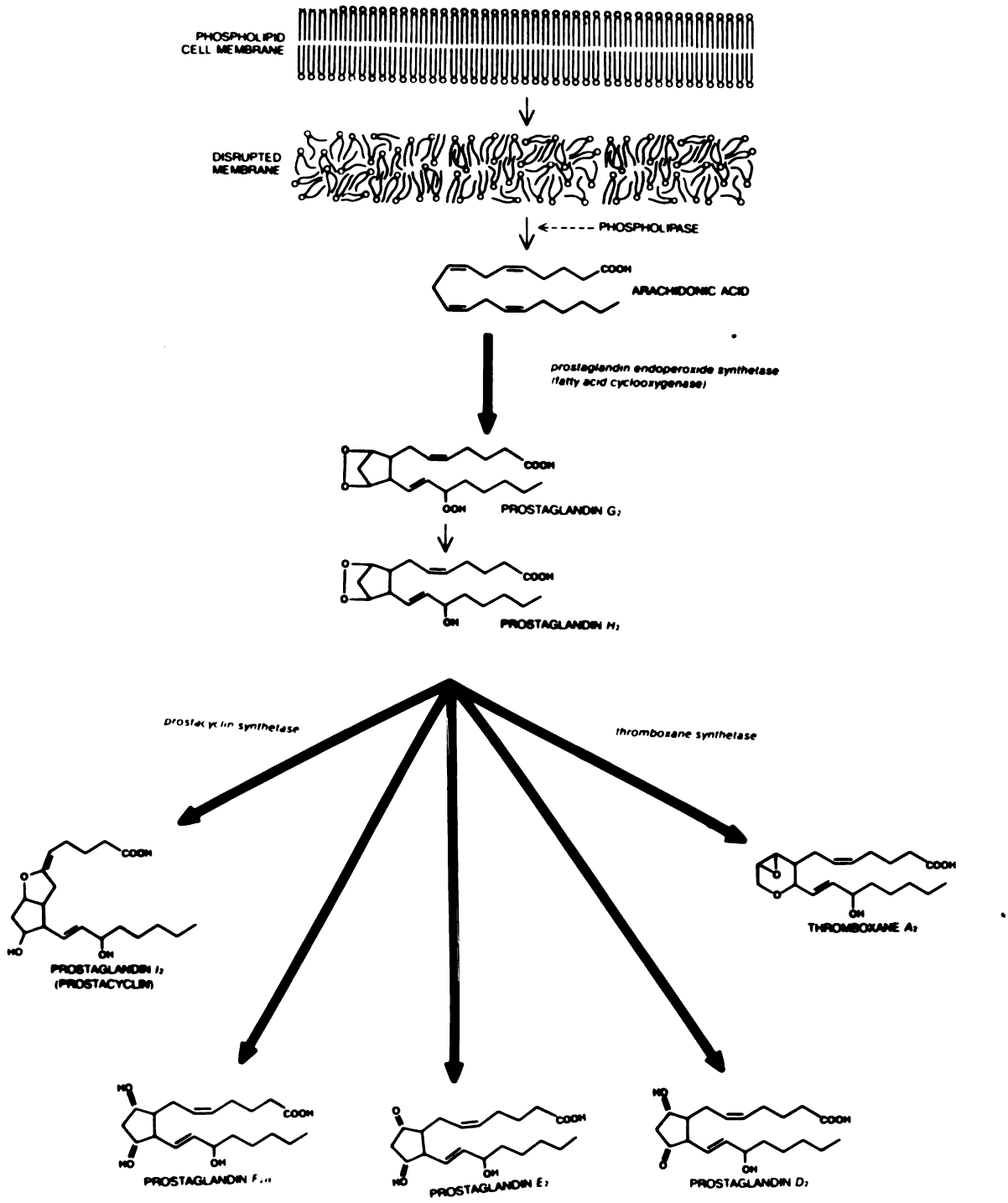
found in phospholipid components of animal cell membranes. In 1973, Hamberg and Samuelsson (73) discovered two labile arachidonic acid metabolites (prostaglandin G_2 and prostaglandin H_2) that could be transformed into other prostaglandins. One of these cyclic endoperoxide metabolites was described in 1975 by Hamberg et al. (74) and was called thromboxane A_2, a potent vasoconstrictor and aggregator of platelets (74). In 1976, Vane et al. (130) isolated prostaglandin I_2 (prostacyclin), a prostaglandin formed mainly by endothelial cells and capable of preventing platelet aggregation as well as producing vasodilatation.

Prostaglandins and prostanoids are derived from essential fatty acids. The most common prostaglandin, the bisenoic (prostaglandin E_2, prostaglandin $F_{2\alpha}$, prostaglandin D_2, prostaglandin I_2 and TXA_2) are derived from arachidonic acid or from linoleic acid after elongation of the carbon chain to 20 units. The monoenoic prostalandins (prostaglandin E_1, etc) are derived from dihomo-γ-linolenic acid and the trienoic prostaglandins (prostaglandin E_3, etc.) are derived from 5, 8, 11, 14, 17 - eicosapentaenoic acid (130). The production of the most common bisenoic prostaglandins from arachidonic acid are depicted in Figure 1.

Thromboxanes and most prostaglandins that reach the systemic circulation are rapidly inactivated in the lungs (10, 56, 137) and gastrointestinal prostaglandins that

Figure 1. Biosynthetic pathway of the major bisenoic prostaglandins and thromboxanes.

Fig. 1


PHOSPHOLIPID CELL MEMBRANE
DISRUPTED MEMBRANE
PHOSPHOLIPASE
ARACHIDONIC ACID
prostaglandin endoperoxide synthetase (fatty acid cyclooxygenase)
PROSTAGLANDIN G2
PROSTAGLANDIN H2
prostacyclin synthetase
thromboxane synthetase
PROSTAGLANDIN I2 (PROSTACYCLIN)
THROMBOXANE A2
PROSTAGLANDIN F2α
PROSTAGLANDIN E2
PROSTAGLANDIN D2

reach the hepatic portal circulation can be inactivated by the liver (56). Prostaglandin I_2 appears not to be metabolized by the lungs (4, 76) but can be converted to biologically inactive metabolites by the liver and kidneys (127, 138).

Prostaglandin synthesis occurs throughout the small intestine (1, 15, 25, 55, 85, 91, 92, 93, 126) and in both muscle and epithelial layers (93). In 1979 LeDuc and Needleman (93) characterized prostaglandin production in the canine stomach and intestinal tract. In the gastric mucosa, the major arachidonic acid metabolites were prostaglandin E_2, prostaglandin I_2 and TXA_2 while the gastric muscularis also produced prostaglandin $F_{2\alpha}$. In the small intestine, the mucosa contained relatively low cyclooxygenase activity but was found to be rich in both prostacyclin and thromboxane synthetase. This was determined by incubating mucosal microsomes with prostaglandin H_2 which resulted in substantial production of both prostaglandin I_2 and TXA_2 while arachidonic acid produced relatively low levels of these two prostaglandins. The major prostaglandins produced by the intestinal muscularis were found to be prostaglandin I_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$. Finally, the colonic muscularis produces prostaglandin I_2 and prostaglandin E_2 while the mucosa produced large quantities of TXA_2 and some prostaglandin I_2. Prostaglandin D_2 was also produced by all tissue preparations but in minute quantities.

In vivo studies indicated that prostaglandin E and prostaglandin F are released from the "resting" intestinal tract (134) and in response to various stimuli such as acetylcholine (119), mechanical stimulation (15), luminal distention (140), and feeding (45). Dupont *et al.* (45) found that concentrations of prostaglandin E_1, prostaglandin E_2, and prostaglandin $F_{2\alpha}$ increase in the gastrointestinal tract of miniature swine following ingestion of a liquid nutrient meal. Furthermore, prostaglandin concentrations in various anatomical locations of the gastrointestinal tract correlated strongly with the time required for the movement of ingestia through the respective regions of the gastrointestinal tract. For example, gastric prostaglandin production increased 30 minutes after feeding and fell 60 minutes after feeding while jejunal prostaglandin production remained unchanged for sixty minutes but subsequently rose thereafter. The authors concluded that feeding stimulates gastrointestinal prostaglandin production and this may be a local phenomenon.

The various effects of prostaglandins on intestinal motor activity has been extensively characterized, especially for prostaglandins E and F. Sanders *et al.* determined prostaglandin synthesizing capabilities by microsomes of both circular and longitudinal gastrointestinal muscle (118). Prostaglandin I_2, prostaglandin $F_{2\alpha}$, prostaglandin E_2, prostaglandin D_2,

prostaglandin A_2, and thromboxane A_2 levels were determined by thin layer chromatography following incubation of canine microsomal preparations with radiolabeled arachidonic acid. The major prostaglandins formed were prostaglandin I_2, prostaglandin E_2, and prostaglandin $F_{2\alpha}$. Furthermore, all areas of the GI tract except the jejunum produced prostaglandin levels in both longitudinal and circular muscle layers that were the same. In the jejunum, prostaglandin production was greater in the longitudinal muscle. All areas of the gastrointestinal tract also produced low levels of prostaglandin D_2 and prostaglandin A_2 in both muscle layers. The results of this study reinforce earlier works by LeDuc and Needleman (93).

In vitro studies by Bergstrom (12) indicate prostaglandins E and F causes contractions of jejunal segments in the rat, chicken, rabbit and guinea pig. Furthermore, prostaglandin $F_{2\alpha}$ has been shown to contract rabbit and rat duodenal segments (2), stimulate circular muscle contractions in the canine duodenum and ileum (42), and stimulate intestinal motility in the intact canine jejunum (121).

Prostaglandin E_1, and E_2 contract human longitudinal muscle strips but relax or inhibit acetylcholine-induced contractions in the same preparation (9, 10). Furthermore, in whole muscle preparations, prostaglandin E_1, either contracts (79) or relaxes (83) the rat duodenum. It appears that two of the major prostalgandins produced by

intestinal muscle (prostaglandin E and prostaglandin F) are strong modulators of intestinal motor activity. Prostaglandin F stimulates circular muscle, longitudinal muscle, and whole muscle preparations while prostaglandin E stimulates or inhibits motor activity depending on the muscle layer, species, and investigator.

Sanders (117) found that inhibition of endogenous prostaglandin production with indomethacin enhanced the amplitude of spontaneous and acetylcholine-induced contractions of isolated canine intestinal muscle. Other studies have also demonstrated this effect (119). Furthermore, the enhanced mechanical activity was associated with enhanced electrical slow wave amplitude and generation of action potentials. The increase in mechanical activity caused by indomethacin was also accompanied by a decrease in prostaglandin I_2 production, the major prostaglandin produced by intestinal smooth muscle (93, 118). The author concluded that prostaglandin I_2 inhibits both spontaneous and acetylcholine-induced contractions of intestinal smooth muscle at physiological production levels and this may be due to an electrical mechanism.

Prostaglandin synthesis inhibition with indomethacin has also been shown to significantly enhance the inhibitory effects of either sympathetic nerve stimulation or exogenous norepinephrine on ileal motility in the guinea pig (7). Furthermore, this effect is reversed by giving

prostaglandins E_1, and E_2 (7, 120); that is, both prostaglandins inhibit the effects of sympathetic stimulation. In addition to the inhibition of the inhibitory effects of sympathetic stimulation on motility, prostaglandin E has also been shown to inhibit both spontaneous and acetylcholine-induced contractions of canine circular muscle (116) and acetylcholine-induced contraction of human longitudinal muscle strips (9, 10).

Sanders (116) also reported that indomethacin increased the magnitude of either acetylcholine or potassium-induced canine ileal contractions. However, Bartho (7) reported that indomethacin inhibited cholinergically initiated ileal contractions in whole guinea pig ileal preparations. It is not clear why this discrepancy exists, however, Sanders primarily used only circular muscle preparations whereas other investigators use whole muscle preparations. It seems that circular muscle from most species reacts differently to some prostaglandins. Undoubtedly, the data regarding the effects of various prostaglandins or prostaglandin synthesis inhibitors on intestinal motor activity are confusing, contradictory, and arcane. These discrepancies may be due to differences in the prostaglandins used (for example Type I vs. Type II or PGE vs. PGF), specific areas of the small intestine, species, or methodology.

In addition to the effects of prostaglandins on autonomic modulations of intestinal motor activity, prostaglandins have also been shown to inhibit serotonin (50) and cholecystokinin (142) induced contractions of isolated guinea pig ileal smooth muscle. It seems that prostaglandins are capable of regulating intestinal motility via either direct actions on intestinal smooth muscle or indirectly by altering neural and humoral inputs to the gut.

Prostaglandins have also been shown to alter gastrointestinal absorption and secretion (5, 29, 60, 70, 84, 100, 101, 102, 104, 111, 112). Prostaglandin E_2, has been shown to increase water, Na^+ , Cl^- , and HCO_3^- secretion in the human jejunum (29, 100, 104, 112) and to decrease glucose absorption in the human (101, 102) and dog jejunum (84). Granger et. al (70) studied the effects of prostaglandin E, on water absorption, lymph flow and transcapillary protein flux in the cat ileum. They found that Prostaglandin E, increased secretion in the ileum as well as lymph flow and protein transport across the capillary endothelial lining. Their studies also indicate gross damage to the intestinal microvilli membrane following prostaglandin E_1 administration.

Prostaglandin $F_{2\alpha}$ has also been shown to increase water and protein secretion (111) and to decrease glucose absorption (5) in the canine jejunum. The previous study (5) also showed decreases in glucose absorption by prostaglandin E_2.

Endogenous prostaglandin synthesis has also been implicated in the control of gastric secretion. Arachidonic acid, the precursor of type II prostaglandins, has been shown to inhibit both pentagastrin and histamine stimulated HCl secretion in the rat stomach (60). Furthermore, these effects were blocked by indomethacin indicating that endogenous prostaglandins were involved. Prostaglandin E_1 is most likely involved since it has been shown to be a powerful inhibitor of gastric acid secretion (95).

These studies indicate that intestinal prostaglandins are capable of inhibiting intestinal glucose absorption and stimulating secretion. The biological diversity of prostaglandins is exemplified by their ability to inhibit secretions in the stomach (60, 95) while stimulating secretions in the small intestine (29, 70, 100, 104, 112, 111).

Prostaglandins are powerful vasoactive agents in the intestinal vascular bed. The role of prostaglandins in regulating resting intestinal blood flow appears to favor the vasodilators since prostaglandin synthesis inhibitors decrease intestinal blood flow in rabbits (18), cats (119),

humans (107) and dogs (33, 63, 65). It is interesting to note, however, that indomethacin inhibits the contractile effects of norepinephrine on rat mesenteric artery strips (96).

Individual prostaglandins have variable effects on intestinal blood flow both in direction and magnitude. Chapnick et al. (33) determined the effects of a variety of prostaglandins on intestinal blood flow in the dog. Over the dose range used, prostaglandin D_2 caused dose dependant decreases in blood flow through the superior mesenteric artery. Decreases in blood flow ranged from 24-64% and were rapid in onset and short in duration. In addition, prostaglandin $F_{2\alpha}$ also produced dose dependant decreases in intestinal blood flow ranging from 30-80%. These effects were also short in duration and rapid in onset. Prostaglandin I_2 increased intestinal blood flow in a dose dependant fashion which ranged from 33-133%. The stable metabolite of prostaglandin I_2, 6-keto-prostaglandin $F_{1\alpha}$, had no significant affect on blood flow thus indicating that the effects of prostaglandin I_2 were not the result of metabolites. Prostaglandin E_2 was also a powerful vasodilator increasing intestinal blood flow 43-112%.

Dusting et al. (47) also studied the effects of various prostaglandins on mesenteric perfusion pressure in constant flow preparations in the dog. They found prostaglandin I_2, prostaglandin E_2, and the cyclic endoperoxide prostaglandin H_2 were vasodilators and TXA_2

was a powerful vasoconstrictor, similar in potency to norepinephrine. They also found prostaglandin $F_{2\alpha}$ to be a very weak vasoconstrictor which is different from that observed by other investigators (5, 33, 51, 110) who generally found prostaglandin $F_{2\alpha}$ to be a moderate or powerful vasoconstrictor. Prostaglandin $F_{2\alpha}$ has also been shown to decrease intestinal oxygen consumption in the dog (110) and this may be a possible mechanism of the most commonly observed vascular effects (5, 33, 51, 110).

Prostaglandin D_2 appears to exert variable effects on the intestinal circulation. Dose dependant decreases in intestinal blood flow have been observed when prostaglandin D_2 is given by single bolus injections into the superior mesenteric artery of the canine (33). Constant infusions, however, have been shown to produce biphasic responses (58). Blood flow initially decreased, returned to control, and then rose substantially above preinfusion values. Furthermore, Fondacaro et al. (58) found that during the hyperemic phase of prostaglandin D_2 administration, blood flow was redistriubted away from the mucosa and toward the muscularis. Intestinal oxygen uptake was also reported to increase during prostaglandin D_2 infusions (58).

Prostaglandin I_2 is a vasodilator in the small intestine (33, 47, 58, 110). Its stable metabolite, 6-keto-prostaglandin $F_{1\alpha}$, is not vasoactive when bolus injections are given into the superior mesenteric artery

(33). It has also been shown that the hyperemia caused by prostaglandin I_2 is directed mainly to the mucosal bed (58, 110). Furthermore, prostaglandin I_2 has been shown to increase intestinal oxygen uptake (58, 110).

Prostaglandins, therefore, appear to be powerful modulators of intestinal blood flow. It is not clear, however, if such observed vascular effects are physiological or merely pharmacological. Furthermore, prostaglandins may exert their vascular effects by direct actions on vascular smooth muscle, indirect actions such as metabolism or influences on the release of vasoactive substances, or both.

Recent evidence suggests that prostaglandins may act via their own receptors (54, 75, 97, 103). Greenberg et al. (71) have attempted to characterize the nature of prostaglandin receptors in both rabbit and canine vascular smooth muscle. The contractile responses of vascular smooth muscle strips to various prostaglandins was attenuated or abolished when dithiothreitol was added. Dithiothreitol is a disulfide-reducing agent. Since this effect was specific only for prostaglandin-induced muscle contraction, the authors concludedd that a disulfide-protein complex was a necessary component for the expression of the vascular effects of prostaglandins in vascular smooth muscle.

Arachidonic Acid

There is little or no free arachidonic acid in cells, therefore, synthesis of prostaglandins and thromboxanes require arachidonate release which is mainly esterified to cell phospholipids (96). The major phospholipids involved in arachidonate release by phospholipases appear to be phosphatidylcholine (18) and phosphatidylinositol (7, 27). Furthermore, natural release or addition of exogenous arachidonic acid to cells with prostaglandin synthesis enzymes results in rapid production of prostaglandins (3, 111, 133).

Arachidonic acid could become available for prostaglandin synthesis in the small intestine either by "natural" release from membrane bound phospholipid stores (8, 19, 28, 99) or by absorption from the intestinal lumen (40). Chow and Hollander (40) looked at the mechanisms and factors influencing luminal absorption of arachidonic acid in rat intestinal preparations. This study indicates that arachidonic acid absorption is concentration dependant and does not require metabolic energy since metabolic uncouplers have no effect on absorption rates. Furthermore, absorption was enhanced by disrupting the unstirred water layer, by decreasing the luminal pH and by substituting bile salts for Tween 80. Arachidonic acid absorption decreased when oleic or linoleic acid was added indicating competition with other fatty acids. Finally, arachidonate absorption was not affected by the

addition of amino acids or sugars to the luminal contents. The authors concluded that arachidonic acid was readily absorbed from the small intestine in a dose dependant manner. They also concluded that absorption was via carrier mediated diffusion since Michaelis-Menton saturation Kinetics were observed in the presence of metabolic uncouplers, and various alterations in the luminal environment can alter arachidonic acid absorption.

Arachidonic acid causes a large increase in blood flow through the canine superior mesenteric artery when large bolus injections are given (33). Furthermore, indomethacin abolished this hyperemia. Dusting et al. (47) have observed the same effects of arachidonic acid on perfusion pressure in constant flow preparations in the dog intestine and hindlimb preparation. Dusting et al. (46) also found that arachidonic acid relaxed vascular smooth muscle strips from rabbit and rat mesenteric arteries using the blood bathed organ technique. In addition, they also reported that the same dosages of arachidonic acid contracted these preparations when the prostaglandin substrate was allowed to incubate with blood for 0.1-4 minutes. They attributed the latter response to preferential formation of platelet thromboxanes. Similar results were reported by Kauffman and Whittle (82) using a constant flow gastric preparation in the dog. Bolus injections of arachidonic acid (25-200 mg) into a proximal port (3 seconds transit time) produced a dose dependant decrease in perfusion pressure. The same

dosages, however, given into a distal port (30 seconds transit time) produced dose-dependant increases in perfusion pressure. These studies indicate that arachidonic acid is a vasodilator in the intestinal and gastric vascular beds. These effects are probably due to prostaglandin production and not due to the substrate per se since arachidonic acid-induced vasodilatation can be abolished by indomethacin. Finally, extraneous prostaglandin production by non-intestinal tissues (e.g. platelets) during arachidonic acid administration is capable of altering these effects.

Thromboxane Synthesis and Inhibition

In 1975, Hamberg et al. (74) first described the conversion of prostaglandin G_2 to an unstable prostanoid capable of contracting vascular smooth muscle and aggregating platelets. This prostanoid was originally called rabbit aorta contracting substance (74) but today is better known as thromboxane A_2.

Le Duc and Needleman (93) found that the canine jejunum is capable of producing thromboxane A_2 and only the mucosal layer of the gut wall has the necessary enzyme for thromboxane production. They also found that the jejunal mucosa produces prostaglandin I_2 and imidazole inhibited thromboxane production but did not affect

prostaglandin I_2 production. These investigators determined thromboxane levels in intestinal tissue incubation media by radioimmunoassay.

Moncada et al. (105) examined the effects of imidazole and 21 imidazole derivatives on thromboxane synthesis inhibition in platelets. They found that the concentration of imidazole required to produce 50% inhibition of thromboxane production by platelets (ic_{50}) was 22 ug/ml. All of the imidazole derivatives tested required at least 8 times that concentration to produce 50% inhibition. The authors concluded that the inhibition of thromboxane synthesis by imidazole was more powerful than imidazole derivatives. Furthermore, imidazole selectively inhibited thromboxane synthesis since synthesis of other cyclooxygenase and lipoxygenase products were unaffected.

Another potent and highly selective inhibitor of thromboxane synthesis is Sodium - 5 - (3'-Pyridinylmethyl) Benzofuran - 2 - Carboxylate (U-63557A) recently developed by the Upjohn Company (139). Wynalda et al. (139) examined the effects of U-63557A on thromboxane synthesis inhibition as well as its pharmacokinetics in dogs. Single doses of U-63557A given at 5 $mg \cdot kg^{-1}$ i.v. resulted in a 90% inhibition of plasma thromboxane levels that lasted for over two hours.

Summary

The postprandial intestinal hyperemia is a complex physiological phenomenon and many factors are involved. Such factors include gastrointestinal hormones, the products of food digestion, histamine, and possibly endogenous prostaglandins.

Prostaglandins are capable of modulating many intestinal functions such as absorption, secretion, motor activity, metabolism, and blood flow. Given that prostaglandins are capable of such alterations in the physiology of the intestine and given that prostaglandin synthesis inhibition has significant effects on the food-induced increases in intestinal blood flow and oxygen uptake (63), it seems likely that endogenous intestinal prostaglandins play a significant role in the postprandial intestinal hyperemia. Therefore, this possibility warrants further investigation. The purpose of this study was to determine the effects of the prostaglandin precursor, arachidonic acid, on the postprandial intestinal hyperemia. In addition, the effects of selective inhibition of thrombane synthesis on the postprandial intestinal hyperemia was also examined.

METHODS AND MATERIALS

Surgical Preparation

All experiments were conducted on mongrel dogs (14-31 kg) of both sexes which were deprived of food for 24 hours. The animals were anesthetized by intravenous injections of pentobarbital sodium at an initial dosage of 30 mg/kg and supplemented as needed to maintain a surgical plane of anesthesia. All animals were ventillated with a positive-pressure respirator (Harvard Apparatus, Millis, MA) that was adjusted to achieve normal arterial blood pH (7.39 $\pm$ 0.02), O_2 tension (87.9 $\pm$6.6), and CO_2 tension (37.5 $\pm$ 2.4) before each experiment. Systemic arterial blood pressure was continuously monitored through a cannula in the femoral artery.

The abdominal cavity was exposed via a midline incision and either one or two segments of the jejunum about 25 cm aboral to the ligament of Treitz were exteriorized. Care was taken to ensure that the autonomic nerves were intact. After a rubber tube was placed into the lumen of each segment for placement and withdrawal of solutions, both ends of the segment(s) were tied and cut away from the adjacent jejunum to exclude collateral flow. Luminal pressure was recorded by connecting the rubber tube to a pressure transducer (Statham P23Gb) when a solution was present in the lumen. Before cannulation of blood vessels, heparin sodium (500 $U \cdot kg^{-1}$) was administered

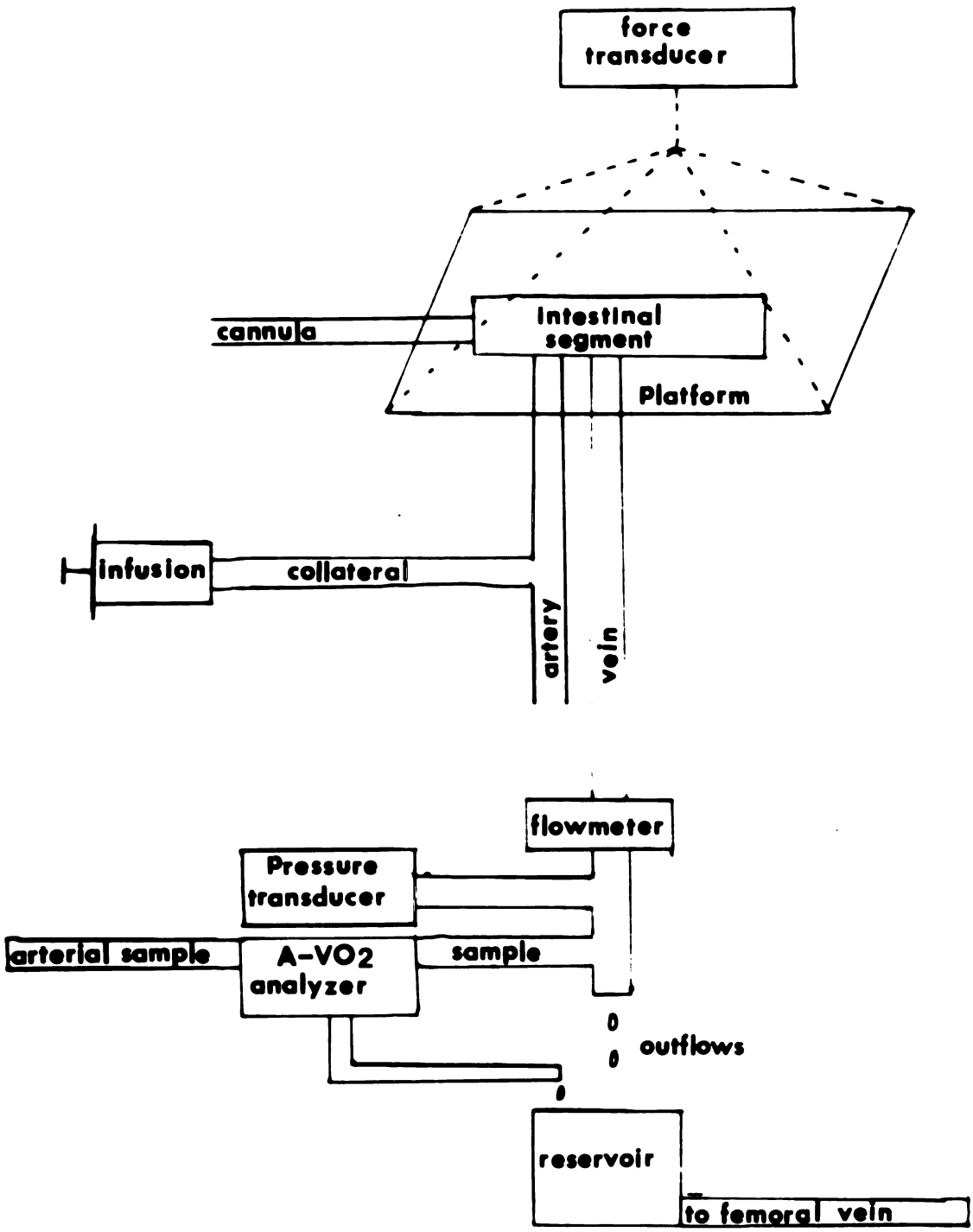
intravenously. The exteriorized jejunal segments were kept moist with saline soaked gauze and a clear plastic sheet and maintained at 37° C with a heat lamp and temperature probe. At the end of all experiments, the animals were euthanized by an overdose of pentobarbital sodium. Figure 2 schematically represents the methodological and surgical interventions in most of these experiments. Details of individual series of experiments are described later.

Preparation of Solutions

The food solution used contained equal parts by weight of fat, carbohydrate, and protein. It was prepared by adding 30 g high-fat test diet, 15 g high-protein test diet, and 5 g high-carbohydrate test diet (US Biochemical Cleveland, OH) to 400 ml of 0.1 N $NaHCO_3$ containing 750 mg of a pancreatic enzyme preparation (Viokase, VioBin, Monticello, IL). The mixture was then mixed gently with a magnetic stirrer at room temperature for 5 h to permit digestion. Before the experiment, nine parts of digested food were mixed with one part of gallbladder bile, and the pH and osmolality of the mixture were adjusted with either $NaHCO_3$ or HCl and NaCl, respectively [pH 7.1 $\pm$ 0.1; osmolality 316 $\pm$ 5 mosmol/kg (n = 35)]. Both the digested food plus bile and the normal saline were kept at 37° C during the experiment.

Figure 2. Schematic representation of the preparation used in most experiments.

Fig. 2


force transducer
cannula
intestinal segment
Platform
infusion
collateral
artery
vein
flowmeter
Pressure transducer
arterial sample
A-VO2 analyzer
sample
outflows
reservoir
to femoral vein

Arachidonic acid, sodium salt (Sigma Chemical Co., St. Louis, MO) was prepared immediately before use. Solutions were prepared by dissolving appropriate quantities in a 0.9% NaCl solution and subjecting the solution to sonic disruption to aid the dissolution process. Mefenamic acid (Park Davis, Detroit, MI) was prepared by adding appropriate quantities to a 0.9% NaCl solution and the pH was raised with 1.0 M NaOH until the drug went into solution. (pH 8.4 $\pm$ 0.2, n = 10). Imidazole (Sigma Chemical Co., St. Louis, MO) and U-63557A (Sodium 5- (3'-Pyridinylmethyl) Benzofuran - 2 - Carboxylate, a gift from the Upjohn Co., Kalamazoo, MI) were prepared by dissolving appropriate amounts in 0.9% NaCl solutions.

Experimental Protocol

Eleven series of experiments were performed (n = 89). In Series I (n = 14), the effects of various doses of arachidonic acid on jejunal vascular resistance were determined in constant flow preparations before and after mefenamic acid administration (a cyclooxygenase inhibitor). A single jejunal segment was exteriorized and the single artery perfusing the segment was cannulated. The segment was perfused at a constant rate with the aortic blood by interposing a Masterflex pump (Cole-Parmer Instruments, Chicago, IL) between the local intestinal artery and a femoral artery. The perfusion pressure was monitored via a catheter in the perfusion line attached to a pressure

transducer (Statham P236b). Pump flow rate was adjusted until perfusion pressure was 10 mmHg below the systemic arterial pressure and then maintained constant throughout the experiment. Once a steady state had been reached, arachidonic acid (AA), sodium salt (Sigma Chemical, St. Louis, MO), or its carrier solution, 0.9% NaCl, was infused upstream from the pump with a Harvard infusion pump set at various infusion rates ranging from 1.0 to 267 $\mu g \cdot min^{-1}$. The AA concentration of the infusate ranged from 0.5 to 2.3 mM, and the volume rate of infusion never exceeded 0.75 $ml \cdot min^{-1}$. The transit time for AA between the site of infusion and the gut loop was less than 5 s. Each infusion lasted until perfusion pressure reached a steady level. At the end of each experiment, the rate of pump blood flow was measured, and local blood concentration of AA achieved at each infusion rate was calculated from the pump blood flow rate and infusion rate.

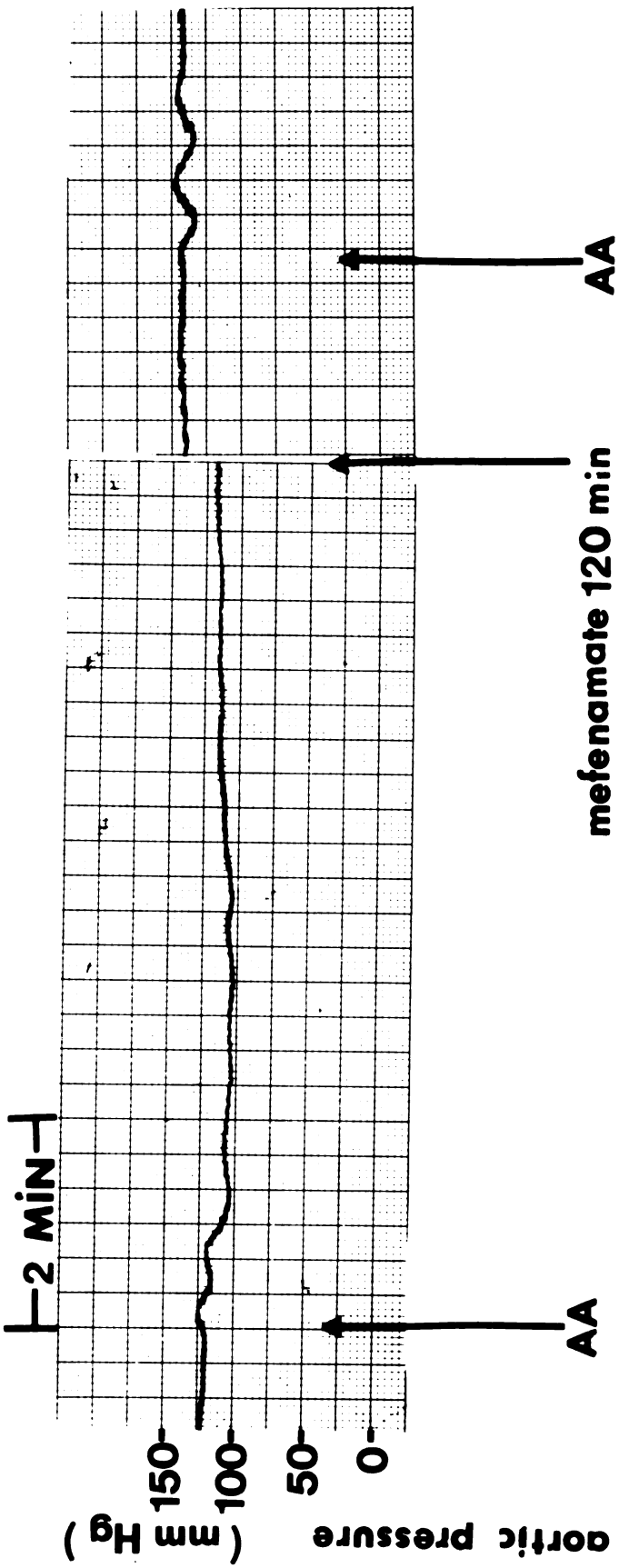
In seven dogs in this series, cyclooxygenase inhibitors were also used to determine whether the effects of AA were due to AA per se or its metabolites, i.e., prostaglandins. The animals were pretreated 48 hours before the experiment with acetylsalicilic acid (oral, 25 mg/kg, Sigma Chemical, St. Louis, MO) and the vascular response to AA was tested by infusing solutions of various concentrations of arachidonic acid into the arterial inflow line as previously described. Acetylsalicylic acid was used to preferentially inhibit cyclooxygenase in blood

tissues. A Swan-Gantz catheter was then advanced into the pulmonary artery via a femoral vein. A single i.v. bolus injection of arachidonic acid (300 ug/kg) was given and the resulting drop in aortic pressure was noted. Mefenamic acid was then infused intravenously at a dosage of 10 mg/kg for 10 min. Two hours later, another i.v. bolus injection of arachidonic acid (300 ug/kg) was given. If aortic pressure was unaffected by the arachidonic acid injection, then the vascular response to arachidonic acid was tested as described above. Figure 3 represents the effects of intra-pulmonary injections of arachidonic acid on aortic pressure before and two hours after mefenamic acid administration.

In Series II (n = 7), the effect of i.v. infusions of arachidonic acid (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) on the postprandial jejunal hyperemia was examined. The single vein draining the single segment preparation was cannulated for measurement of venous outflow by timed collection with a stopwatch and graduated cylinder. Blood flow was also continuously monitored by an extracorporeal flow transducer (BL 2048-E04, Biotronex Laboratories, Silver Spring, MD) placed in the venous outflow line and connected to an electromagnetic flowmeter (BL610, Biotromex Laboratories). The venous outflow was directed into a reservoir held at 37^{o} C, and the blood returned to the animal via a catheter in the femoral vein at a rate equal to the venous outflow. Ten milliliters of normal saline was placed into the lumen

Figure 3. Polygraph chart recording showing the effect of a single bolus of arachidonic acid (300 $\mu g \cdot kg^{-1}$) given into the pulmonary artery on aortic pressure. This was done before and 120 min after i.v. infusion of mefenamic acid (10 $mg \cdot kg^{-1}$).

Fig. 3


aortic pressure (mm Hg)
150
100
50
0
2 MIN
AA
mefenamate 120 min
AA

for 15 min. This procedure was repeated 4-5 times until blood flow reached a steady state, at which time the luminal contents were changed to digested food. The change in blood flow due to food was determined as the difference in steady-state flows during luminal placement of normal saline and digested food. After determining the response to food, AA was infused intravenously at a rate of 40 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with a Harvard dual-infusion pump (Harvard Apparatus). When blood flow reached a steady state, the response due to food was again measured as described above during the AA infusion. The infusion of AA lasted 30 min and the total dose of AA given was 1200 $ug \cdot kg^{-1}$. The carrier solution, 0.9% NaCl, was infused intravenously at 0.76 ml/min as a control, and the response due to food was measured during the infusion.

In Series III (n = 8), the effect of i.a. infusions of arachidonic acid (4-8 $\mu g \cdot ml\ blood^{-1}$) on the postprandial jejunal hyperemia was examined. The same protocol was used as described in Series II, but AA was infused into a side branch of the single artery of the segment at 0.2 ml/min. The carrier solution infused at the same rate served as a control. The vascular response to luminal placement of digested food was determined before and after AA infusion as in Series II.

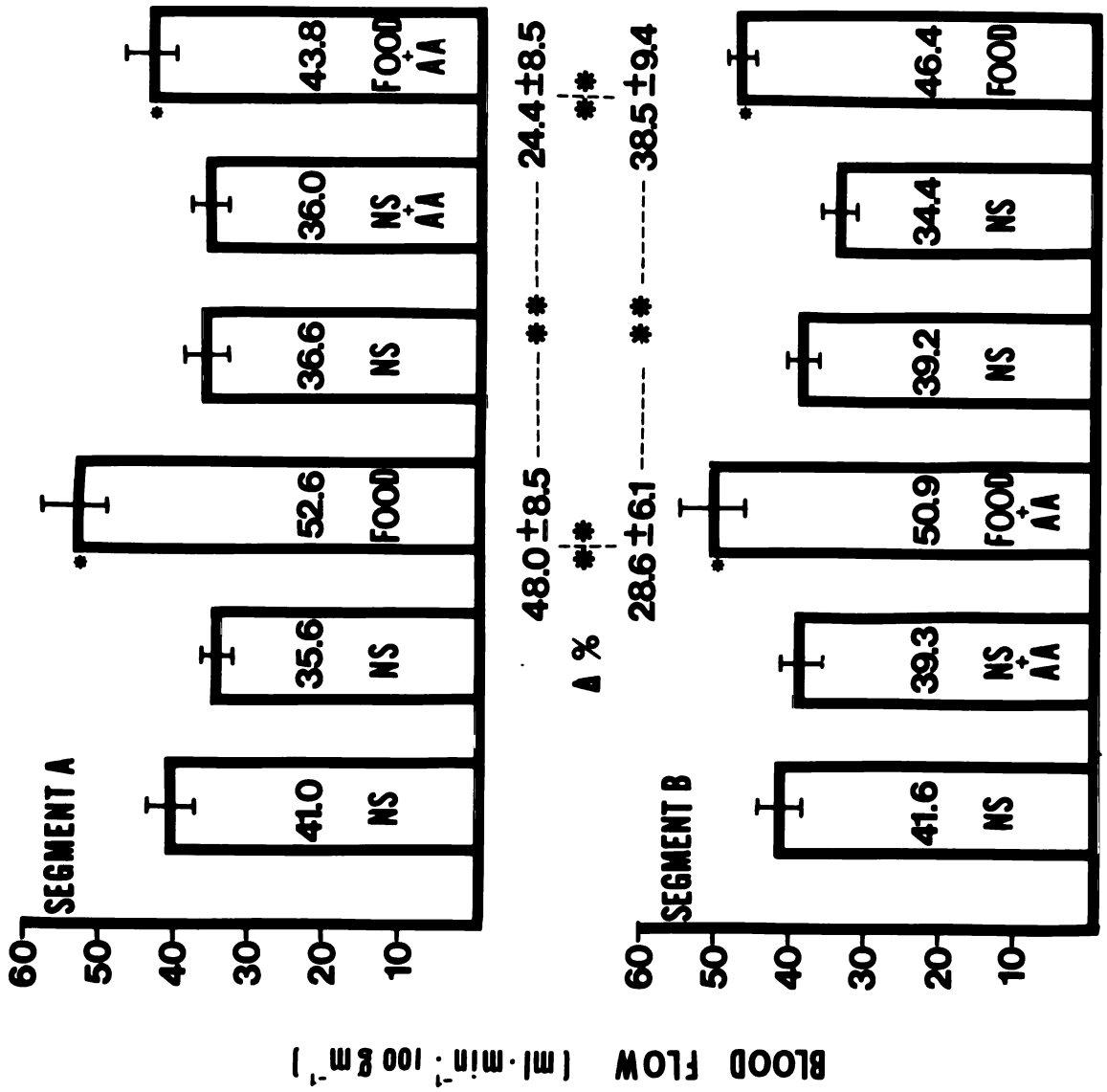
In Series IV (n = 12), the effects of luminal placement of arachidonic acid on the food-induced increases in jejunal blood flow and oxygen uptake were determined.

Two jejunal segments were isolated, the vein draining each segment was cannulated, and the venous outflows were measured as described above. When blood flows reached a steady state after repeated placements of normal saline to both segments, the vascular response to food was tested in both segments. The protocol for this series of experiments is shown in Fig. 4. At different 15-min periods, the lumen of each segment contained normal saline, normal saline plus AA, food, and food plus AA. The concentration of AA in the mixtures was 6.5×10^{-4} M (200 ug/ml). All solutions were subjected to sonic disruption for at least 5 min to ensure homogenous dissolution before placement into the jejunal lumen. Before placement of the next solution, the lumens were thoroughly and gently rinsed with normal saline and flows to both segments were allowed to attain a steady state. In five dogs, the arterial and venous outflow blood samples were obtained for the measurement of blood O_2 content by a Lex-O_2-Con-TL O_2 content analyzer (Lexington Instruments, Waltham, MO). Jejunal O_2 uptake was calculated as the product of venous outflow and arteriovenous O_2 content difference.

Series V (n = 3) was conducted to determine if changes in jejunal blood flow by mechanical means would change jejunal oxygen uptake. The purpose was to determine whether changes in O_2 uptake observed in other experiments are blood flow dependent. A loop of the jejunum was exteriorized as above. The single artery supplying the

Figure 4. Mean venous outflows from 2 adjacent jejunal segments containing normal (NS), NS plus arachidonic acid (AA), food, or food plus AA. Values shown below or above 2 adjacent bars indicate percent differences in flow between 2 bars. * $P < 0.05$ relative to preceding value. ** $P < 0.05$ between 2 values denoted by dotted line. n = 12.

Fig. 4


SEGMENT A
SEGMENT B
BLOOD FLOW (ml·min⁻¹·100 g m⁻¹)
60
50
40
30
20
10
41.0
NS
35.6
NS
52.6
FOOD
36.6
NS
36.0
NS
+AA
43.8
FOOD
+AA
41.6
NS
39.3
NS
+AA
50.9
FOOD
+AA
39.2
NS
34.4
NS
46.4
FOOD
Δ %
48.0±8.5
24.4±8.5
28.6±6.1
38.5±9.4
*
**

segment was cannulated, and a perfusion circuit with an interposed pump (Masterflex) was established between a femoral artery and the single segmental artery. The circuit was designed so that the jejunal segment could be alternately perfused by the pump set at various flow rates or naturally by systemic arterial pressure. Under natural perfusion conditions, blood flow was altered by adjusting a variable clamp on the inflow line. Perfusion pressure was monitored through a cannula inserted into the arterial circuit. The single vein draining the segment was cannulated. Arteriovenous O_2 content difference was determined continuously by perfusing femoral arterial blood and a portion of the venous outflow at 6 ml/min through separate cuvettes of an arteriovenous O_2 content difference analyzer (A-VOX Systems, San Antonio, TX) with a Gilson pump (Minipuls 2, Gilson Medical Electronics, Middleton, WI). The arteriovenous O_2 content difference analyzer had been calibrated with a Lex-O_2-Con TL O_2 content analyzer (Lexington Instruments, Waltham, MO). The venous outflow and outflows from the cuvettes were allowed to drain into a reservoir. The blood in the reservoir was pumped back to the animal via a femoral vein at a rate equal to the total outflows. Venous outflow was measured by timed collection of the outflow. Intestinal O_2 uptake was calculated as the product of venous outflow and arteriovenous O_2 difference. The time required for venous blood to reach the arteriovenous O_2 analyzer was 35 s and was compensated for

by the calculation of O_2 uptake. After all measured variables had stabilized for 20-30 min, the effects of reductions in blood flow under natural flow conditions on O_2 uptake were determined by stepwise increases in arterial inflow occlusion. The perfusion circuit was then switched to pump perfusion, and the effects of pump-induced alterations in blood flow on O_2 uptake were determined. The effects of changes in flow on O_2 uptake were studied twice under natural and pump perfusion in each dog. After each experiment, the jejunal segments were weighed and all data were normalized to 100 g of tissue.

In Series VI (n = 7), the effects of i.a. infusions of arachidonic acid (4-8 ug·ml blood^{-1}) on the food-induced increases in jejunal blood flow and oxygen uptake were determined after administration of a cyclooxygenase inhibitor. Mefenamic acid was infused intravenously over a 10 min period at 10 mg·kg^{-1}. Two hours after the end of the infusion, the cyclooxygenase block was tested as previously described in Series I (Figure 3). The effects of i.a. infusions of arachidonic acid on the food-induced increases in jejunal blood flow and oxygen uptake were then determined. Jejunal O_2 uptake was determined as previously described in Series V.

In Series VII (n = 14), the effects of imidazole (Sigma Chemical Co., St. Louis, MO) on the food-induced increases in jejunal blood flow and oxygen uptake were determined. Imidazole was infused intra-arterially at a

rate of 5 mg/min designed to achieve a blood concentration of approximately 100 ug/ml, which has been shown to effectively block thromboxane production (45). The food-induced increases in jejunal blood flow and oxygen uptake were determined before and during imidazole infusions. The imidazole infusion lasted for 30 min. and the total dose of imidazole was 150 mg.

In Series VIII (n = 5), another inhibitor of thromboxane synthesis was used. The protocol was identical to Series VII except the selective thromboxane synthetase inhibitor U-63557A (Upjohn, Kalamazoo, MI) was used in place of imidazole. U-63557A was given intravenously at a dosage of 5.0 mg/kg.

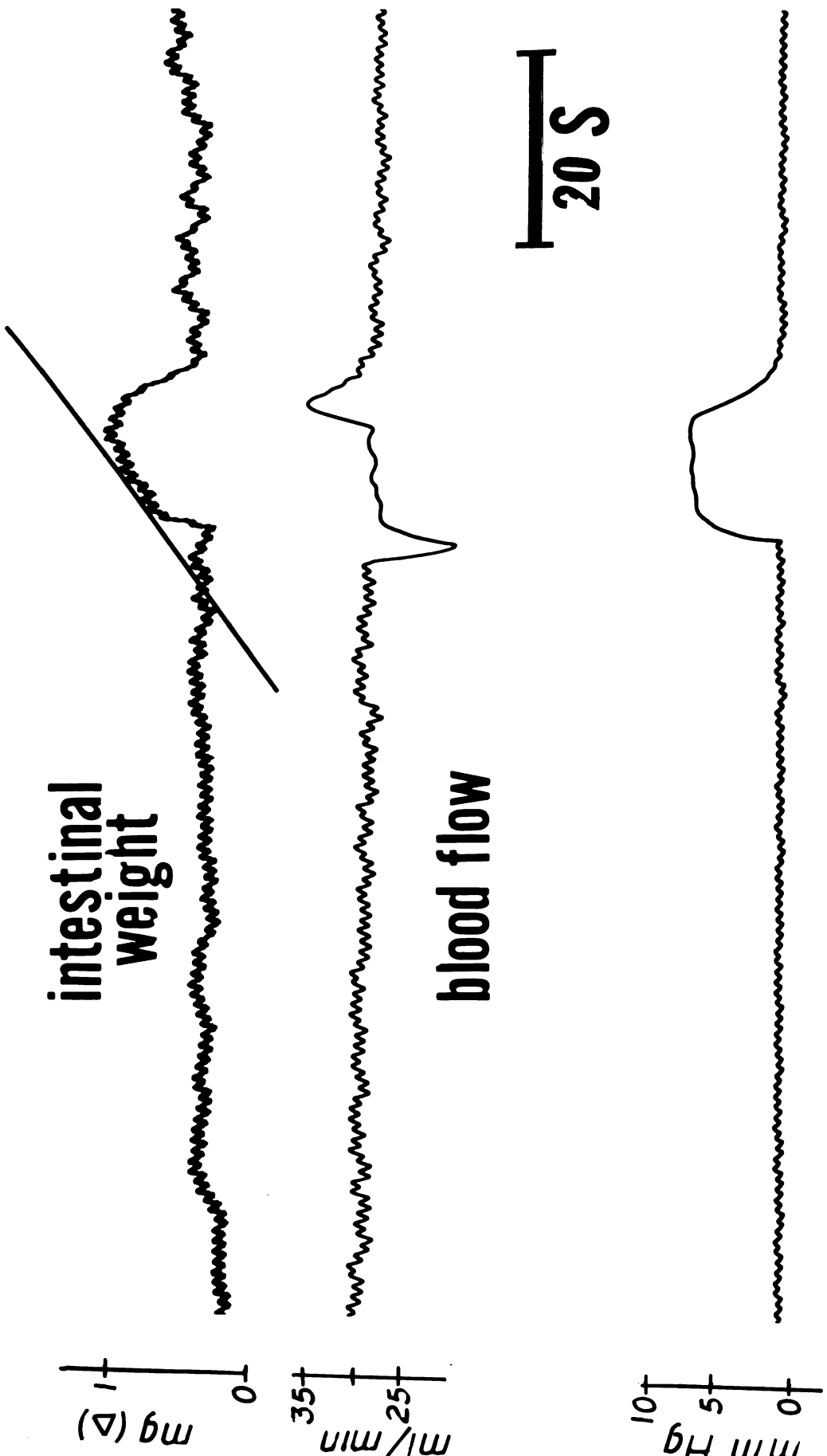
In Series IX, the effects of imidazole and U-63557A on glucose absorption were determined in seven and five dogs, respectively. A jejunal segment was isolated, the vein draining the segment was cannulated, and the venous outflows were measured as described above. Arterial and venous blood samples were obtained before and after luminal placement of food for determination of plasma glucose concentration with a glucose oxidase glucose analyzer (Yellow Springs Instrument Company, Yellow Springs, OH). This was repeated after i.a. infusions of imidazole ($5\ mg \cdot min^{-1}$) and after i.v. infusions of U-63557A ($5\ mg \cdot kg^{-1}$). Glucose absorption was calculated as the product of blood flow and the venous-arterial glucose content difference and expressed as $mg \cdot min^{-1} \cdot 100g^{-1}$.

Glucose absorption during food placement was expressed as the difference in glucose absorption before and during luminal placement of digested food.

In Series X, the capillary filtration coefficient (CFC) was determined gravimetrically in 6 dogs. A jejunal segment was isolated as before and placed on a platform vertically suspended from a force displacement transducer (FT 03B, Grass Instruments). The venous outflow was continuously monitored until a steady state was achieved. CFC was determined after a sudden elevation of venous pressure (to approximately 10 mm Hg lasting approximately 10-15 seconds) which precipitated a change in intestinal weight. The weight gain due to venous pressure elevation was characterized by two distinct components: an initial rapid increase due to venous capacitance filling and a more prolonged phase of weight gain assumed to represent capillary filtration. The point of demarcation between these two phases was obtained by observing where venous flow equilibration occurs. Venous outflow falls initially upon raising venous pressure but subsequently attains a plateau lower than the control value. This flow equilibration point represents the end of the blood volume shift, and measuring the rate of intestinal weight gain from this point provides an estimate of capillary filtration rate (Figure 5). The slope of the filtration component of the jejunal weight gain was divided by the

Figure 5. Original polygraph chart recording of the data used to estimate jejunal capillary filtration coefficient (CFC). Solid line (intestinal weight panel) represents the rate of tissue water accumulation following the blood volume shift used in estimating CFC.

Fig. 5


intestinal weight
blood flow
venous pressure
20 S
mg (Δ)
1
0
ml/min
35
25
mm Hg
10
5
0

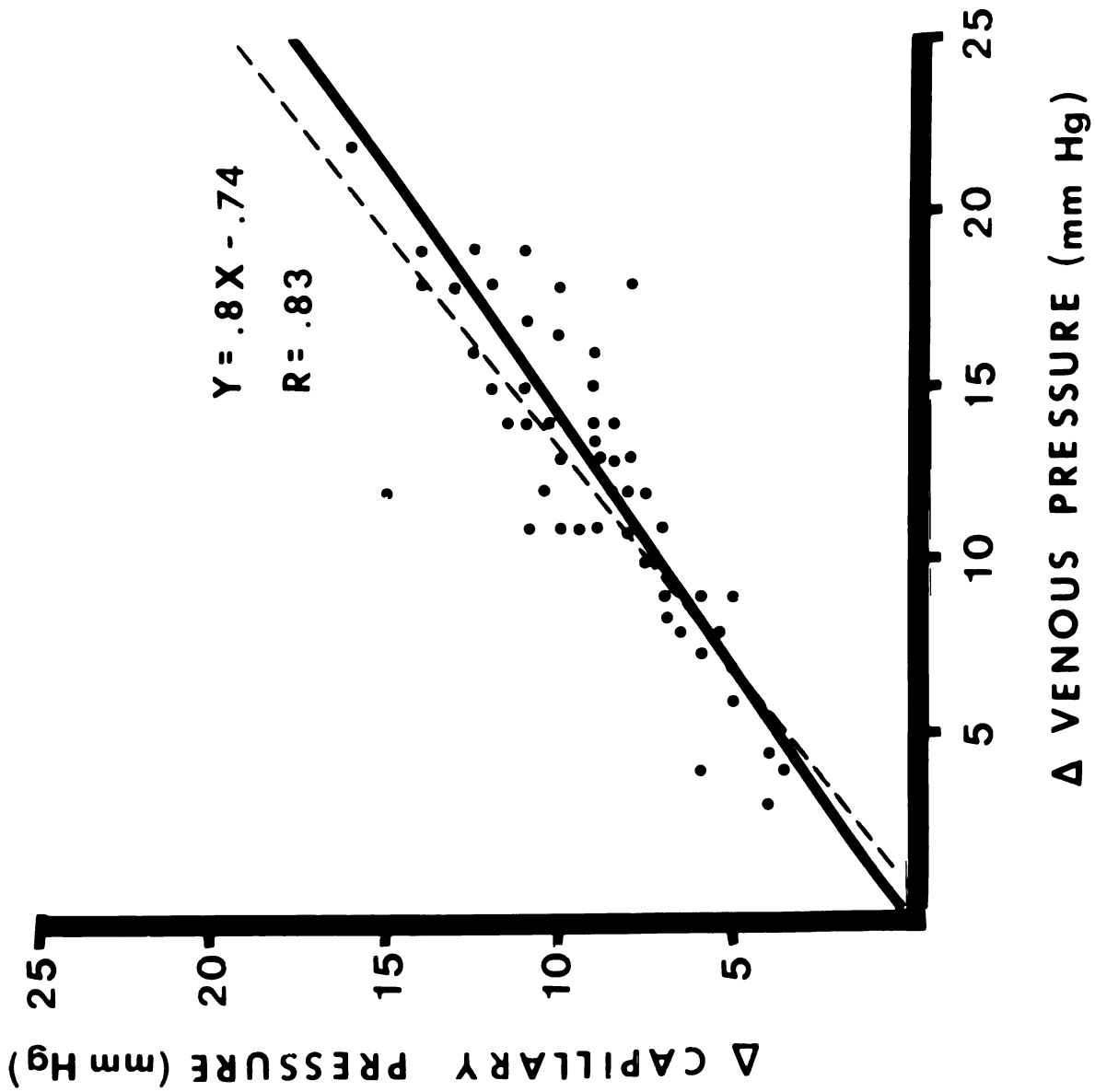
change in capillary pressure. In all experiments, the increase in venous pressure had no affect on the intestinal fluid volume.

In estimating capillary pressure, we assumed a 70% transmission of the imposed venous pressure change to the exchange vessles. To validate this assumption, four additional experiments were performed in which capillary pressures were measured during a wide range of venous pressure changes. Capillary pressures were estimated using the venous occlusion technique as previously described by Granger et al. (68). As can be seen in Figure 6, the percent transmission of the imposed venous pressure change to the capillaries is tightly adherent to the line assuming 70 percent transmission. This is especially evident between venous pressure changes of 10 and 15 mm Hg, which is the range in which our experiments were conducted.

Jejunal capillary filtration coefficients were determined both before and during intra-arterial imidazole (5 mg/min) infusions with either saline or digested food in the jejunal lumen. Furthermore, multiple CFC readings were obtained throughout the food placement period (16 min) both before and during imidazole infusions in order to profile time dependent changes in jejunal CFC during nutrient absorption.

Figure 6. Correlation between changes in venous pressure and changes in capillary pressure in isolated jejunal segments. Dotted line represents the observed regression line of the data, solid line represents 70% transmission of the imposed venous pressure elevations to the exchange vessels.

Fig. 6


Y=.8X-.74
R=.83
Δ CAPILLARY PRESSURE (mm Hg)
Δ VENOUS PRESSURE (mm Hg)
5
10
15
20
25

In Series XI (n = 6), the jejunal CFC was determined before and after food placement as previously described in Series X. Then mefenamic acid (10 mg/kg IV) was given, and after two hours, the above procedure was repeated.

Treatment of Data

All blood flow, oxygen uptake, and glucose absorption data were normalized to 100g tissue weight. Some data were expressed as percent change from control or absolute change between treated and control groups. Most of the data were expressed as the mean $\pm$ S.E.M.

The statistical procedures used in analyzing the data were the Students' t test modified for comparison of two sample means, analysis of variance, linear-regression analysis, the ordinary least-squares technique, polynomial analysis for multiple correlation, the variance ratio test, and the chi-square test for normality of frequency distribution. Statistical significance was set at $P < 0.05$.

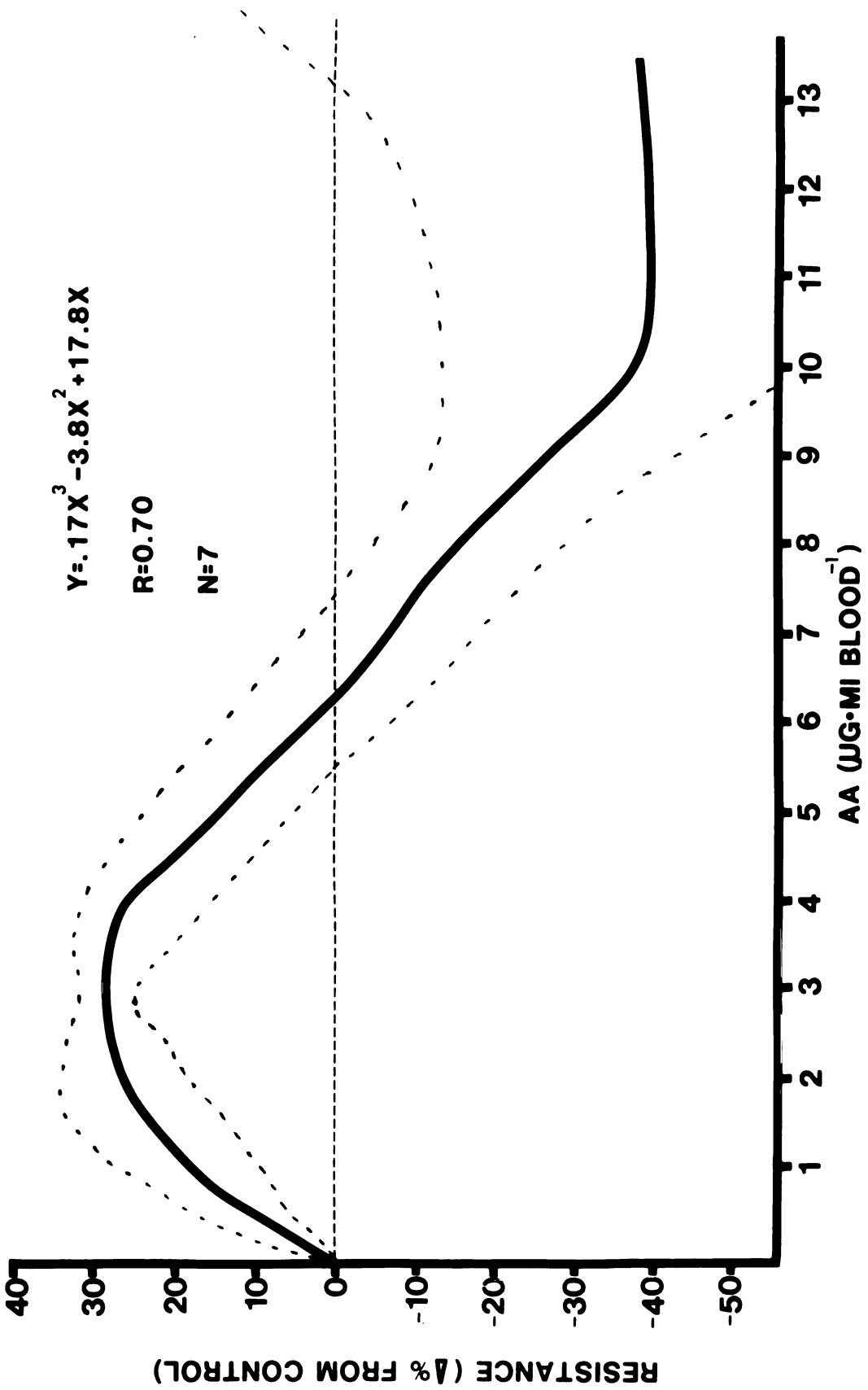
RESULTS

Systemic arterial pressure 123 ± 7 mm Hg (n = 84) was not significantly altered by intravenous or intra-arterial infusions of arachidonic acid, imidazole, U-63557A, or their carrier solutions. Furthermore, systemic arterial pressure was not altered by luminal placement of arachidonic acid or digested food. Systemic arterial pressure was reduced by bolus injections of arachidonic acid into the pulmonary artery at 300 ug/kg but returned toward control within approximately 6 minutes (Figure 3). Intravenous infusions of mefenamic acid in Series 6 and 11 significantly increased aortic blood pressure from 129 ± 5.0 mm Hg to 150 ± 9.0 mm Hg. All experiments, however, were conducted under steady state conditions of aortic pressure.

Figure 7 shows the effects of local intra-arterial infusions of AA on jejunal vascular resistance when the local arterial AA concentration was raised from 0 to 13 $\mu g \cdot ml\ blood^{-1}$ from circulating levels already present (Series 1). The control jejunal vascular resistance was 2.13 ± 0.18 $mmHg \cdot ml^{-1} \cdot min \cdot 100\ g^{-1}$. Infusion of the drug carrier, 0.9% NaCl, at the same rates of infusion as AA did not significantly alter jejunal vascular resistance. An increase in local arterial AA concentrations to a range between 1.0 and 5.7 $\mu g \cdot ml\ blood^{-1}$ significantly increased vascular resistance whereas an increase in the concentration between 8.0 and 13.0 $\mu g \cdot ml\ blood^{-1}$

Figure 7. Effects of intra-arterial infusion of arachidonic acid on jejunal vascular resistance. Dotted lines indicate a zone of 95% confidence. n = 47 from 7 dogs. AA, arachidonic acid.

Fig. 7


Y=.17X³-3.8X²+17.8X
R=0.70
N=7
RESISTANCE (Δ% FROM CONTROL)
40
30
20
10
0
-10
-20
-30
-40
-50
1
2
3
4
5
6
7
8
9
10
11
12
13
AA (μG·ml BLOOD⁻¹)

significantly decreased vascular resistance. The data were analyzed by a digital computer utilizing 47 data points from seven animals using the ordinary least-squares technique, which resulted in a third-order polynomial equation that was 70% correlated with the data points. Upper and lower boundaries for each dosage were computed using the parameter covariance matrix and t values such that $P < 0.05$. Lumen pressure of the jejunal segments was not significantly altered at all infusion rates.

Figure 8 shows the effects of local intra-arterial infusions of AA on jejunal vascular resistance before and after mefenamic acid in the 7 dogs pretreated with aspirin 48 hours prior to the experiment. Before mefenamic acid, i.a. infusions of arachidonic acid produced dose dependant decreases in jejunal vascular resistance. After mefenamic acid (10 $mg \cdot kg^{-1}$), however, the same dogs were completely refractory to the effects of i.a. infusions of arachidonic acid on jejunal vascular resistance (solid regression line). Aspirin pretreatment, therefore, abolished the vasoconstrictor effect of AA at low doses (Figure 7) and aspirin pretreatment and mefenamic acid prevented all vascular effects of AA on jejunal vascular resistance (Figure 8).

Table 1 and Table 2 show the effects of intra-arterial (5-8 $\mu g \cdot ml\ blood^{-1}$) and intravenous (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) infusion of AA on food-induced jejunal hyperemia, respectively. Intra-arterial infusion of AA did not

Figure 8. Effects of intra-arterial infusions of various doses of arachidonic acid on jejunal vascular resistance before and after mefenamic acid (10 mg/kg, i.v.) in dogs pretreated with a single oral dose of aspirin (25 $mg \cdot kg^{-1}$) 48 h before the experiemnt. The dashed line represents the effects of arachidonic acid on jejunal vascular resistance before mefenammic acid (triangles are actual data points) and the solid line indicates the effects of arachidonic acid on jejunal vascular resistance after mefenamic acid (circles are actual data ponts). The regression coefficients are significantly different at $P < 0.05$, $n = 51$ from 6 dogs, AA = arachidonic acid.

Fig. 8

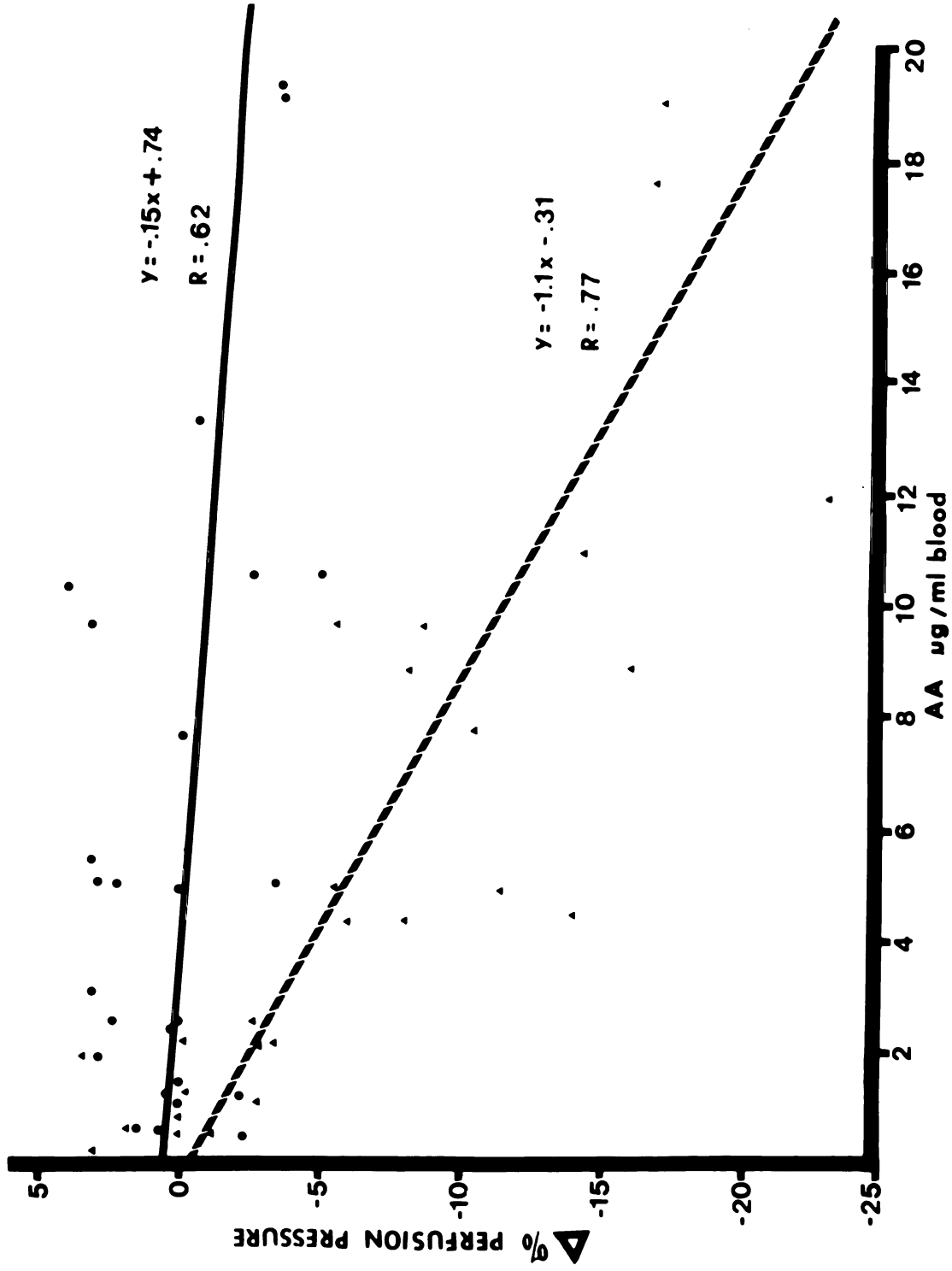

Y=-.15x+.74
R=.62
Y=-1.1x-.31
R=.77
Δ% PERFUSION PRESSURE
AA ug/ml blood
5
0
-5
-10
-15
-20
-25
2
4
6
8
10
12
14
16
18
20

Table 1. The effects of intra-arterial infusions of arachidonic acid (AA) on the postprandial intestinal hyperemia. Blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P < 0.05$ relative to the corresponding value before infusion, n=7.

TABLE 1

Lumen Content	Flow	Δ Flow	Δ % Flow
Before AA infusion			
Saline	36.8±2.5		
		20.1±3.9*	54.3±9.2*
Food	56.9±5.5		
During AA infusion			
Saline	36.8±5.4		
		8.4±2.1*	23.5±5.3*
Food	43.2±7.1		

Table 2. The effects of intravenous infusions of arachindonic acid (AA) on the postprandial intestinal hyperemia. Blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P < 0.05$ relative to the corresponding value before infusion, n=7.

TABLE 2

Lumen Content	Flow	△ Flow	△ %Flow
Before AA infusion			
Saline	37.8±4.1		
		16.8±3.0	44.0±6.6
Food	54.6±6.5		
During AA infusion			
Saline	29.2±1.8*		
		7.58±1.3*	26.8±5.2*
Food	36.8±2.1		

significantly alter control blood flow (Table 1), but intravenous infusion significantly decreased control blood flow from 37.8 to 29.2 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ (Table 2). The dosages for intra-arterial infusion were chosen based on the data from Figure 7 to maintain local arterial concentration within the range of 5-8 µg/ml, whereas the dosage of intravenous infusion was chosen because no systemic or local side effects were observed (46). Regardless of the route of infusion, AA produced the same results. Before intra-arterial or intravenous infusion, luminal placement of digested food significantly increased blood flow by 54.3 or 44.0%. After intra-arterial or intravenous infusion, luminal placement of digested food still significantly increased blood flow, but the hyperemia produced was significantly less than before infusion. This is true whether the data are expressed as absolute change in blood flow (+20.1 $\pm$ 3.9 before vs. +8.4 $\pm$ 2.1 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ after i.a. infusion and +16.8 $\pm$ 3.0 before vs. +7.58 $\pm$ 1.3 $ml \cdot min^{-1} \cdot 100^{-1}$ g after i.v. infusion) or as the percent change from control (+54.3 $\pm$ 9.2 before vs. +23.5 $\pm$ 5.3% after i.a. infusion or +44.0 $\pm$ 6.6 before vs. +26.8 $\pm$ 5.2% after i.v. infusion). In both the intra-arterial and intravenous series, the vascular response to digested food was not significantly affected by infusion of the carrier solution. Food produced a 49.2 $\pm$ 7.9 and 43.2 $\pm$ 8.1% increase in flow before and after the infusion of the carrier.

In Series 4, the effects of luminal placement of AA on both the vascular and metabolic responses to luminal placement of digested food were examined. The vascular responses of the two adjacent jejunal segments to luminal placement of normal saline or digested food with and without AA are depicted in Fig. 4. The concentration of AA, 0.65 mM, was chosen after preliminary studies. The studies indicated that at higher concentrations AA increased intestinal secretion and motility and produced fluctuations in jejunal blood flow. The concentration used, 0.65 mM, was the highest concentration at which the above effects were not observed. As can be seen in Fig. 4, the design of the experiment was to use one segment as the control for the other segment, i.e., in a particular period, one segment contained only normal saline or food alone while the other segment contained one of these solutions plus AA.

Digested food significantly increased blood flow whether or not AA was added to digested food. Although addition of AA to normal saline did not significantly alter blood flow, addition of AA to digested food significantly attenuated the food-induced hyperemia. This is true whether the effects of food alone and food plus AA were compared within the same segment (Figure 4, page 43) (+48 vs. +24.4% in segment A and +38.5 vs. +28.6% in segment B) or between the two segments when each solution was placed simultaneously in each of the two segments (+48 vs. +28.6%

in the third period and +38.5 vs. +24.4% in the last period). Thus AA significantly attenuated the food-induced hyperemia whether AA was administered intra-arterially (Table 1), intravenously (Table 2), or placed into the lumen with food (Fig. 4).

AA also attenuated the food-induced increase in O_2 uptake. As shown in Fig. 9, a 26% increase in O_2 uptake produced by food alone in segment A was significantly greater than that produced by food plus AA in segment A (+9.7%) or segment B (+15.3%). Likewise, a 28.8% increase in O_2 uptake produced by food alone in segment B was significantly greater than that produced by food plus AA in segment A (+9.7%) or segment B (+15.3%). As shown in Fig. 10, there was a significant correlation between the food-induced increases in O_2 uptake and blood flow. This correlation holds for both food alone and food plus AA.

Series 5 determined whether or not the attenuation of the food-induced increases in intestinal oxygen uptake by arachidonic acid resulted from the attenuation of the food-induced increases in blood flow. Figure 11 shows the relation between changes in blood flow and changes in O_2 uptake obtained from three jejunal segments in which flow was altered by a pump. Although a decrease in blood flow from about 34 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ significantly decreased O_2 uptake ($P < 0.05$, analysis of variance), a stepwise increase in blood flow from 34 to 105 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ did not significantly alter O_2 uptake. Thus it appears that O_2

Figure 9. Mean O_2 uptakes from 2 adjacent jejunal segments containing normal saline (NS), NS plus arachidonic acid (AA), food, or food plus AA. Values shown below or above 2 adjacent bars indicate percent differences in O_2 uptake between 2 bars. * $P < 0.05$ relative to preceding value. ** $P < 0.05$ between 2 values denoted by dotted line. n = 5. $\dot{V}O_2$ = O_2 uptake.

Fig. 9

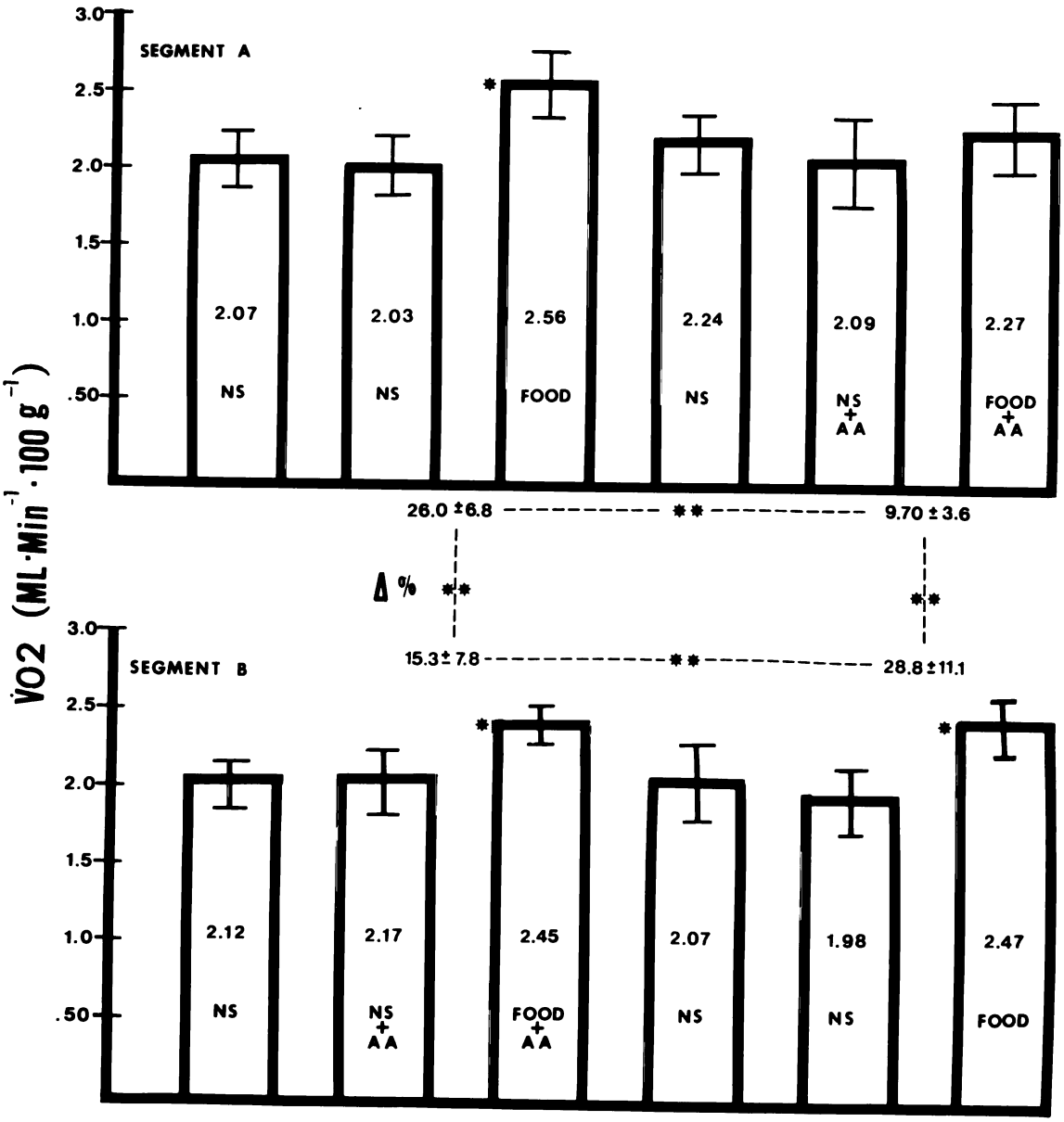

SEGMENT A
3.0
2.5
2.0
1.5
1.0
.50
2.07
NS
2.03
NS
2.56
FOOD
2.24
NS
2.09
NS + AA
2.27
FOOD + AA
26.0 ±6.8
**
9.70 ±3.6
Δ %
**
**
15.3± 7.8
**
28.8 ±11.1
SEGMENT B
3.0
2.5
2.0
1.5
1.0
.50
2.12
NS
2.17
NS + AA
2.45
FOOD + AA
2.07
NS
1.98
NS
2.47
FOOD
V̇O2 (ML·Min⁻¹·100 g⁻¹)

Figure 10. Correlation between changes in food-induced increases in jejunal O_2 uptake and blood flow. Closed circles, food alone; open circles, food plus arachidonic acid (AA).

Fig. 10

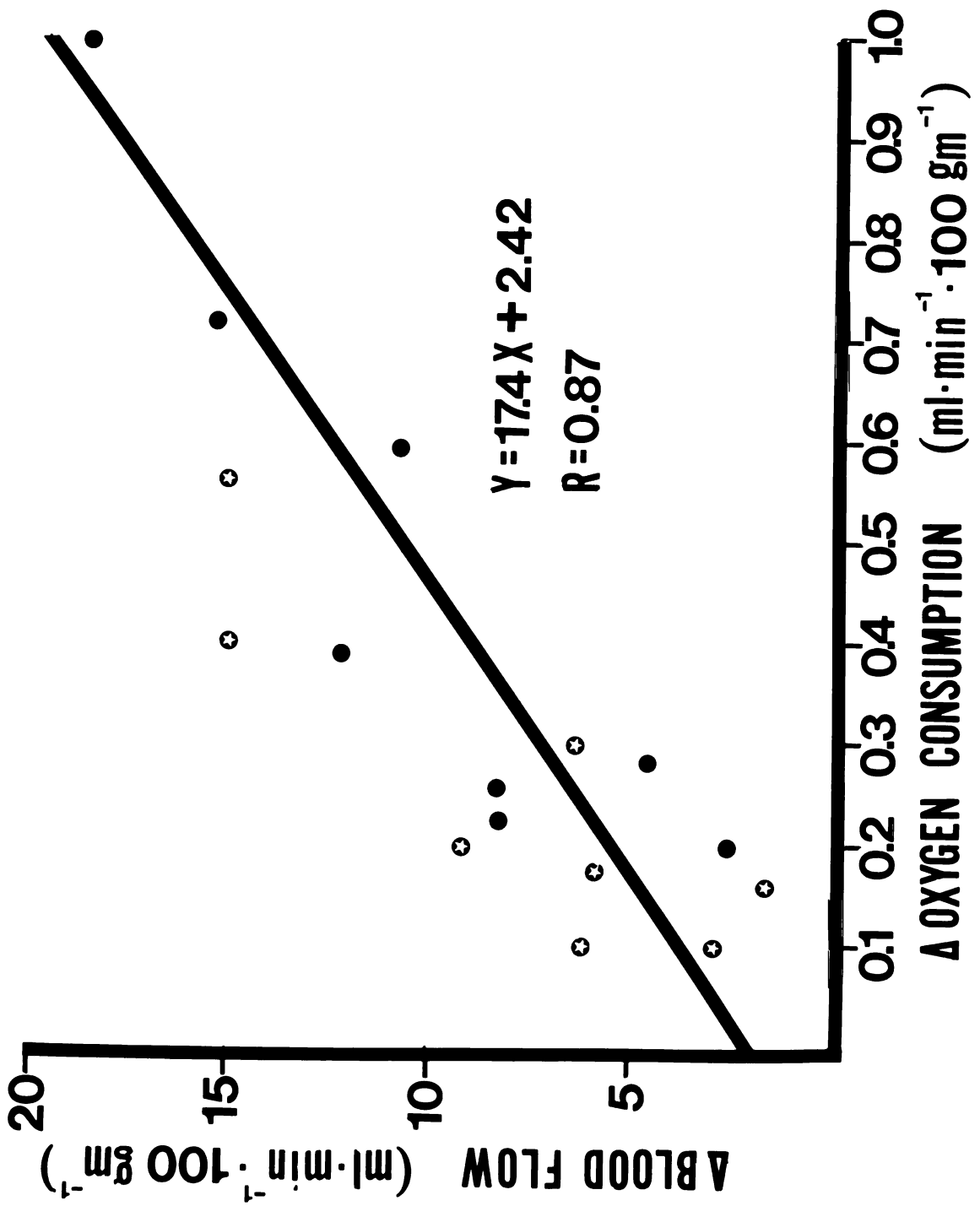
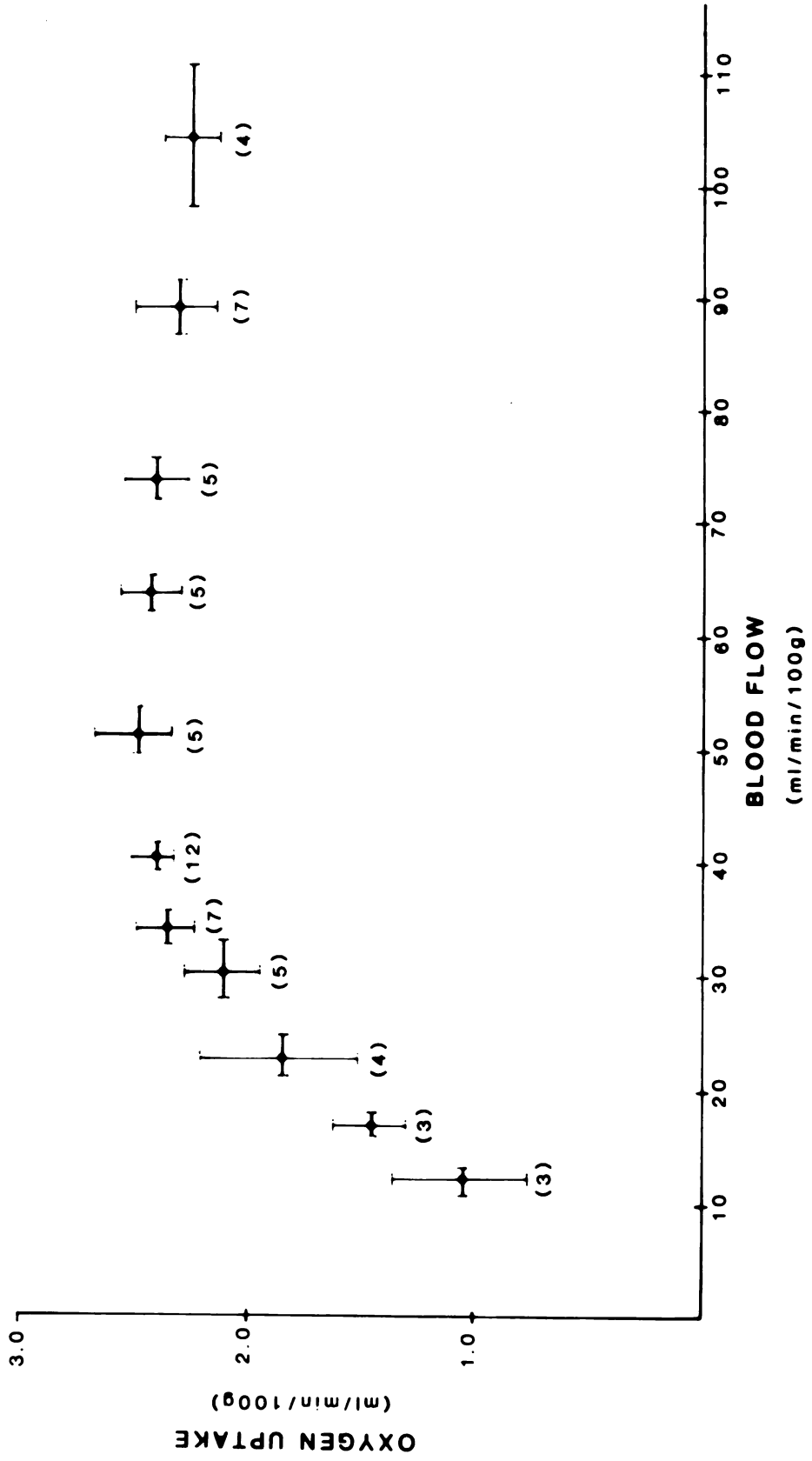

Y=17.4X+2.42
R=0.87
Δ BLOOD FLOW (ml·min⁻¹·100 gm⁻¹)
Δ OXYGEN CONSUMPTION (ml·min⁻¹·100 gm⁻¹)
20
15
10
5
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0.9
1.0

Figure 11. Relation between jejunal blood flow and O_2 uptake. Blood flow was altered mechanically. Numbers in parentheses indicate number of measurements. Resting flow before mechanical alterations was 40.2 $\pm$ 0.5 $ml \cdot min^{-1} \cdot 100g^{-1}$.

Fig. 11


OXYGEN UPTAKE
(ml/min/100g)
3.0
2.0
1.0
BLOOD FLOW
(ml/min/100g)
10
20
30
40
50
60
70
80
90
100
110
(4)
(7)
(5)
(5)
(5)
(12)
(7)
(5)
(4)
(3)
(3)

uptake is independent of blood flow at flow rates above 35 $ml \cdot min^{-1} \cdot 100\ g^{-1}$, but at flow rates below 35 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ O_2 uptake is flow dependent. Resting jejunal blood flows in all experiments performed, except series 2 (Table 2, after i.v. infusions of arachidonic acid), were above the critical value of 35 $ml \cdot min^{-1} \cdot 100g^{-1}$. This indicates that any changes in oxygen uptake due to experimental perturbations were not due to changes in blood flow.

Series 6 was designed to test whether the effects of arachidonic acid on food-induced changes in intestinal blood flow and oxygen uptake were due to the action of arachidonic acid or to its metabolites. The effects of intra-arterial infusions of arachidonic acid on both the metabolic and vascular responses to luminal placement of food were examined after pretreatment with the prostaglandin synthesis inhibitor mefenamic acid. The effectiveness of the cyclooxygenase blockade was tested as previously described (Figure 3). Table 3 illustrates these results. Before arachidonic acid infusions, luminal placement of digested food increased blood flow by 21.3 $ml \cdot min^{-1} \cdot 100g^{-1}$ and oxygen uptake by 0.68 $ml \cdot min^{-1} \cdot 100g^{-1}$. During arachidonic acid infusions, luminal placement of digested food increased blood flow by 18.6 $ml \cdot min^{-1} \cdot 100g^{-1}$ and oxygen uptake by 0.60 $ml \cdot min^{-1} \cdot 100g^{-1}$. The food-induced increases in both intestinal blood flow and oxygen uptake before arachidonic acid administration were not significantly different from those induced after the

Table 3. The effects of intra-arterial infusions of arachidonic acid on the food-induced increases in intestinal blood flow and oxygen uptake after pretreatment with mefenamic acid. $\dot{V}O_2$= oxygen uptake, $\dot{V}O_2$ and blood flow expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$, * $P<0.05$, n=7.

TABLE 3

LUMEN CONTENT

	Saline	Food	Difference
Before Arachidonic Acid:			
Blood flow	32.2 ± 3.3	53.4 ± 8.6	21.3 ± 7.6*
$\dot{V}O_2$	1.86 ± .09	2.54 ± .14	.68 ± .10*
During Arachidonic Acid:			
Blood Flow	33.7 ± 3.5	52.3 ± 8.8	18.6 ± 6.3*
$\dot{V}O_2$	1.91 ± .10	2.50 ± .10	.60 ± .07*

administration. This indicates that the inhibitory effects of arachidonic acid on the food-induced increases in blood flow (Table 1) were due to the products of cyclooxygenase metabolism and not to the arachidonic acid per se.

In Series 7, the effects of imidazole, a selective inhibitor of thromboxane synthesis, on food-induced increases in intestinal blood flow and oxygen uptake were examined in 14 dogs. Figure 12 shows the effects of i.a. infusions of imidazole (5 $mg \cdot min^{-1}$) on the food-induced jejunal hyperemia. Imidazole per se had no effect on resting jejunal blood flow (48.1 $\pm$ 3.1 before imidazole vs. 50.7 $\pm$ .3 $ml \cdot min^{-1} \cdot 100\ g^{-1}$ during imidazole). The food-induced increase in flow was also not affected. This is true whether the data are expressed as absolute change in blood flow (23.0 $\pm$ 3.5 before, vs. 20.4 $\pm$ 2.9 $ml \cdot min^{-1} \cdot 100g^{-1}$ during imidazole infusion) or as the percent change from control (49.8 $\pm$ 7.1 before, vs. 42.0 $\pm$ 6.5% during imidazole infusion). Luminal placement of digested food produced significant increases in jejunal blood flow both before and during imidazole infusions.

Figure 13 shows the effects of i.a. infusions of imidazole on food-induced increases in jejunal oxygen uptake ($\dot{V}O_2$). Imidazole had no effect on resting $\dot{V}O_2$ (2.08 $\pm$ 0.07 before, vs. 2.04 $\pm$ .10 $ml \cdot min^{-1} \cdot 100g^{-1}$ during imidazole infusion) but significantly potentiated the food-induced increase in $\dot{V}O_2$. This is true whether the data are expressed as absolute change (+0.406 $\pm$ .06 before,

Figure 12. Vascular response to luminal placement of food before and during intra-arterial infusions of imidazole. Flow values are means $\pm$ SEM in $ml \cdot min^{-1} \cdot 100g^{-1}$. n = 14, NS, Normal Saline, F, Food, *P < 0.05 relative to before infusion.

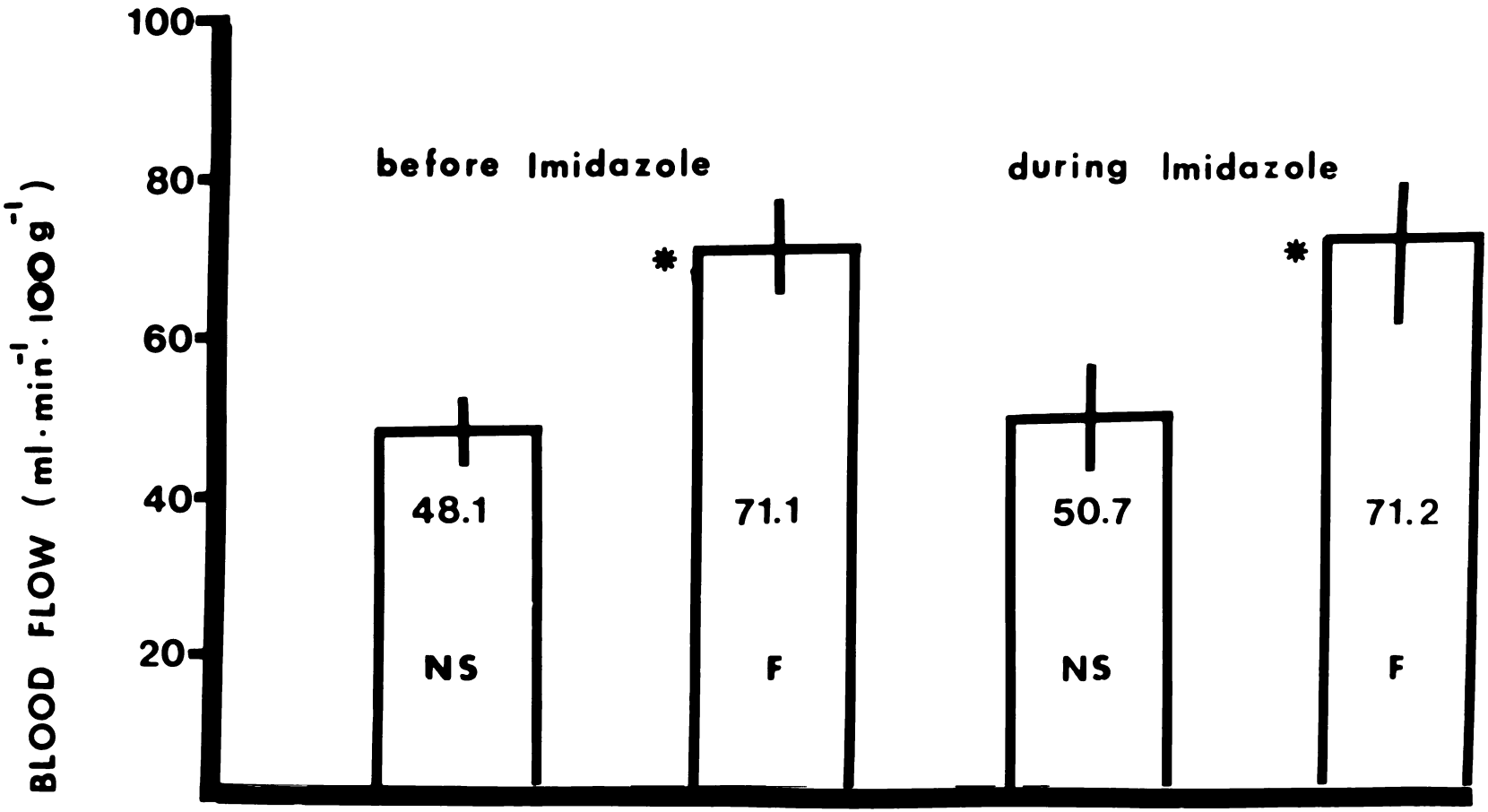


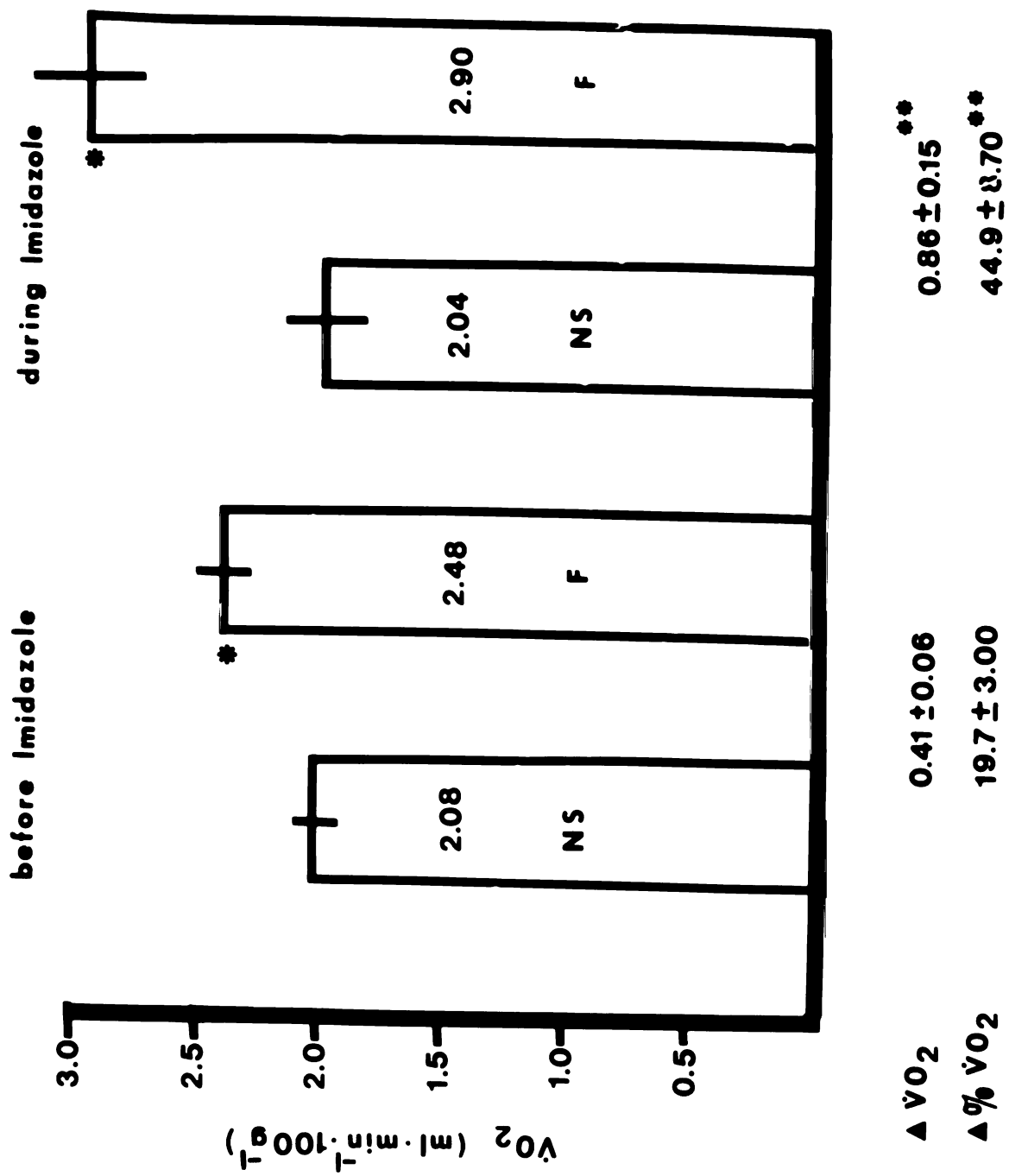
Fig. 12

78

Δ FLOW	23.0 ± 3.5	20.4 ± 2.9
Δ% FLOW	49.8 ± 7.1	42.0 ± 6.2

Figure 13. Effect of intra-arterial infusions of imidazole on the food-induced increases in oxygen uptake. $\dot{V}O_2$, oxxgen uptake, NS, normal saline, F, food. * $P < 0.05$ relative to NS, ** $P < 0.05$ relative to the corresponding value before imidazole. n = 14.

Fig. 13


before Imidazole
during Imidazole
2.08
NS
2.48
F
2.04
NS
2.90
F
3.0
2.5
2.0
1.5
1.0
0.5
V̇O2 (ml·min-1·100g-1)
▲ V̇O2
▲% V̇O2
0.41±0.06
19.7±3.00
0.86±0.15**
44.9±8.70**

vs. +0.858 ± .15 $ml \cdot min^{-1} \cdot 100g^{-1}$ during imidazole infusion) or as percent change from control (+19.7 ± 3.0 before vs. +44.9 ± 8.7% during imidazole infusion). Luminal placement of digested food produced significant increases in $\dot{V}O_2$ both before and during imidazole infusions.

Figure 14 shows the correlations between food-induced increases in jejunal oxygen uptake ($\dot{V}O_2$) and jejunal blood flow before and during imidazole infusion. Changes in the two variables are significantly correlated both before and during imidazole infusions. However, the slopes of the two regression lines are significantly different (2.60 before vs. 0.96 during imidazole infusions). This indicates that for a given food-induced increase in jejunal blood flow, the food-induced increase in jejunal oxygen uptake is significantly greater during imidazole administration than before the administration.

In order to assess whether the effects observed in the above series were a result of thromboxane synthesis inhibition or the action of imidazole per se, experiments were repeated in which U-63557A was substituted for imidazole. This compound is also a selective inhibitor of thromboxane synthesis and has been shown to selectively inhibit thromboxane synthesis at the dosage used (5.0 $mg \cdot kg^{-1}$, i.v.) (139). Table 4 shows the effects of U-63557A on the food-induced increases in both intestinal blood flow and oxygen uptake. U-63557A per se had no effect on

Figure 14. Correlation between percent changes in $\dot{V}O_2$ (oygen uptake) and blood flow elicited by luminal placement of digested food before and during intra-arterial infusions of imidazole. * $P < 0.05$ relative to control.

Fig. 14

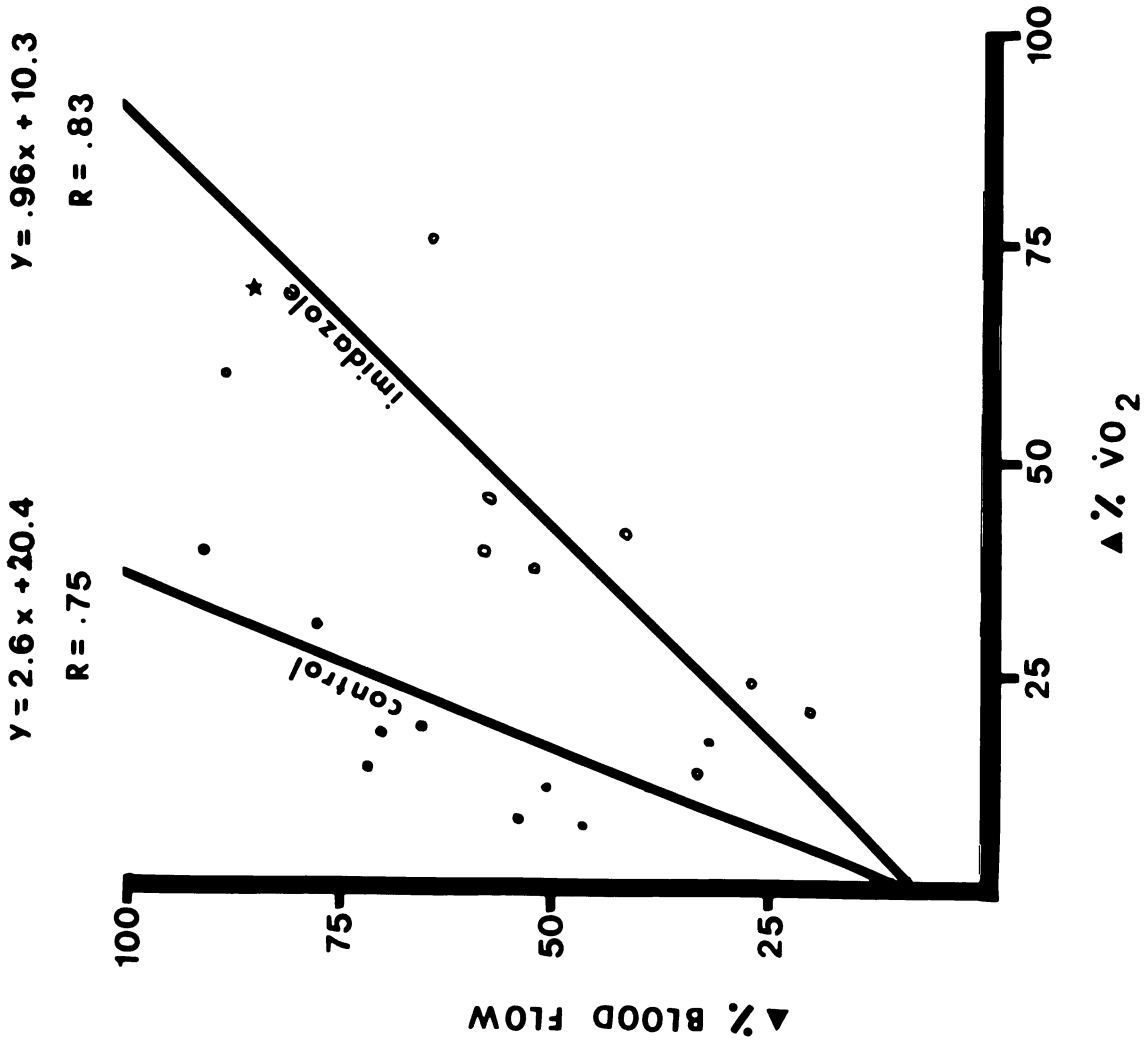

Y = .96x + 10.3
R = .83
Y = 2.6 x + 20.4
R = .75
imidazole
control
100
75
50
25
▲% BLOOD FLOW
100
75
50
25
▲% $\dot{V}O_2$

Table 4. The effects of intravenous infusions of U-63557A on the food-induced increases in intestinal blood flow and oxygen uptake ($\dot{V}O_2$). Values expressed as $ml \cdot min^{-1} \cdot 100g^{-1}$. * P <0.05, 1 = P<0.05 relative to the corresponding value before U-63557A, n=5.

TABLE 4

LUMEN CONTENT

	Saline	Food	△	△ %
Before U-63557A:				
Blood Flow	54.0 ± 4.8	65.2 ± 6.9	11.9 ± 2.9*	21.9 ± 4.4
$\dot{V}O_2$	1.94 ± 0.06	2.29 ± 0.06	0.35 ± 0.08*	19.2 ± 3.5
After U-63557A:				
Blood Flow	42.7 ± 4.9	57.1 ± 8.3	14.2 ± 5.3*	27.5 ± 12.5
$\dot{V}O_2$	1.99 ± 0.10	2.77 ± 0.9	0.78 ± 0.07*[1]	41.6 ± 5.7[1]

the hyperemia. This is true whether the data are expressed as absolute change in blood flow (+11.9 ± 2.9 $ml \cdot min^{-1} \cdot 100g^{-1}$ before U-63557A vs. +14.2 ± 5.3 $ml \cdot min^{-1} \cdot 100g^{-1}$ after U-63557A) or as percent change from control (+21.9 ± 4.4 before U-63557A vs. +27.5 ± 12.5 after U-63557A). Table 4 also shows that U-63557A significantly potentiated the food-induced increase in intestinal oxygen uptake. This is true whether the data are expressed as absolute change in oxygen uptake (+0.35 ± 0.08 $ml \cdot min^{-1} \cdot 100g^{-1}$ before U-63557A vs. +0.78 ± 0.07 $ml \cdot min^{-1} \cdot 100g^{-1}$ after U-63557A) or as percent change from control (+19.2 ± 3.5 before U-63557A vs. +41.6 ± 5.7 after U-63557A). Furthermore, there was a significant correlation between the food-induced increases in intestinal oxygen uptake and blood flow before and after administration of U-63557A. Like the imidazole data (Figure 14, page 83), the slope of the linear regression of the food-induced changes in intestinal oxygen uptake and blood flow before U-63557A treatment was significantly greater ($Y = 0.90 X + 2.5$, $r = 0.95$) than that after the treatment ($Y = 0.46 X - 0.67$, $r = 0.95$). This is also true if the data are expressed as absolute change from control; $Y = 31.8 X + 0.10$, $r = 0.98$ before U-63557A vs. $Y = 9.2 X + 1.27$, $r = 0.73$ after U-63557A. This indicates that for a given food-induced increase in jejunal oxygen uptake (X), the corresponding increase in jejunal blood flow (Y) is significantly less after U-63557A treatment.

Table 5 illustrates the effects of imidazole and U-63557A on jejunal glucose absorption. Before imidazole, the rate of jejunal glucose absorption was 9.6 ± 1.4 $mg \cdot min^{-1} \cdot 100g^{-1}$ and during imidazole infusion the jejunal glucose absorption rate was 12.3 ± 3.2 $mg \cdot min^{-1} \cdot 100g^{-1}$. Furthermore, before U-63557A, the rate of glucose absorption was 11.7 ± 2.6 $mg \cdot min^{-1} \cdot 100g^{-1}$ and after U-63557A, the rate of glucose absorption by the jejunum was 7.64 ± 3.3 $mg \cdot min^{-1} \cdot 100g^{-1}$. Table 5 also shows that jejunal glucose absorption was negative when normal saline was in the lumen. This indicates that the intestine was removing glucose from the arterial blood.

Figure 15 shows the time course of changes in the jejunal capillary filtration coefficient (CFC) during luminal placement of food before and during i.a. infusions of imidazole. Before imidazole and with saline in the lumen, CFC ($ml \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot 100g^{-1}$) was 0.335 ± 0.02. During food placement, CFC rose to 0.401 ± 0.04, 0.428 ± 0.04, 0.410 ± 0.04, and 0.492 ± 0.02, 4, 8, 12, and 16 minutes following food placement, respectively. CFC significantly rose above control after 8 and 16 minutes of food placement. Imidazole <u>per se</u> significantly increased CFC from 0.335 ± 0.02 to 0.446 ± 0.01. Placement of food increased CFC to 0.469 ± 0.03, 0.471 ± 0.04, 0.564 ± 0.07, and 0.595 ± 0.02, 4, 8, 12, and 16 minutes following food placement, respectively. The increased CFC observed 8-16 minutes following food placement were

Table 5. The effects of imidazole (5 $mg \cdot min^{-1}$, i.a.) and U-63557A (5 $mg \cdot kg^{-1}$, i.v.) on jejunal glucose absorption in 7 and 5 dogs, respectively. Values are mean $\pm$ standard error and expressed as $mg \cdot min^{-1} \cdot 100g^{-1}$.

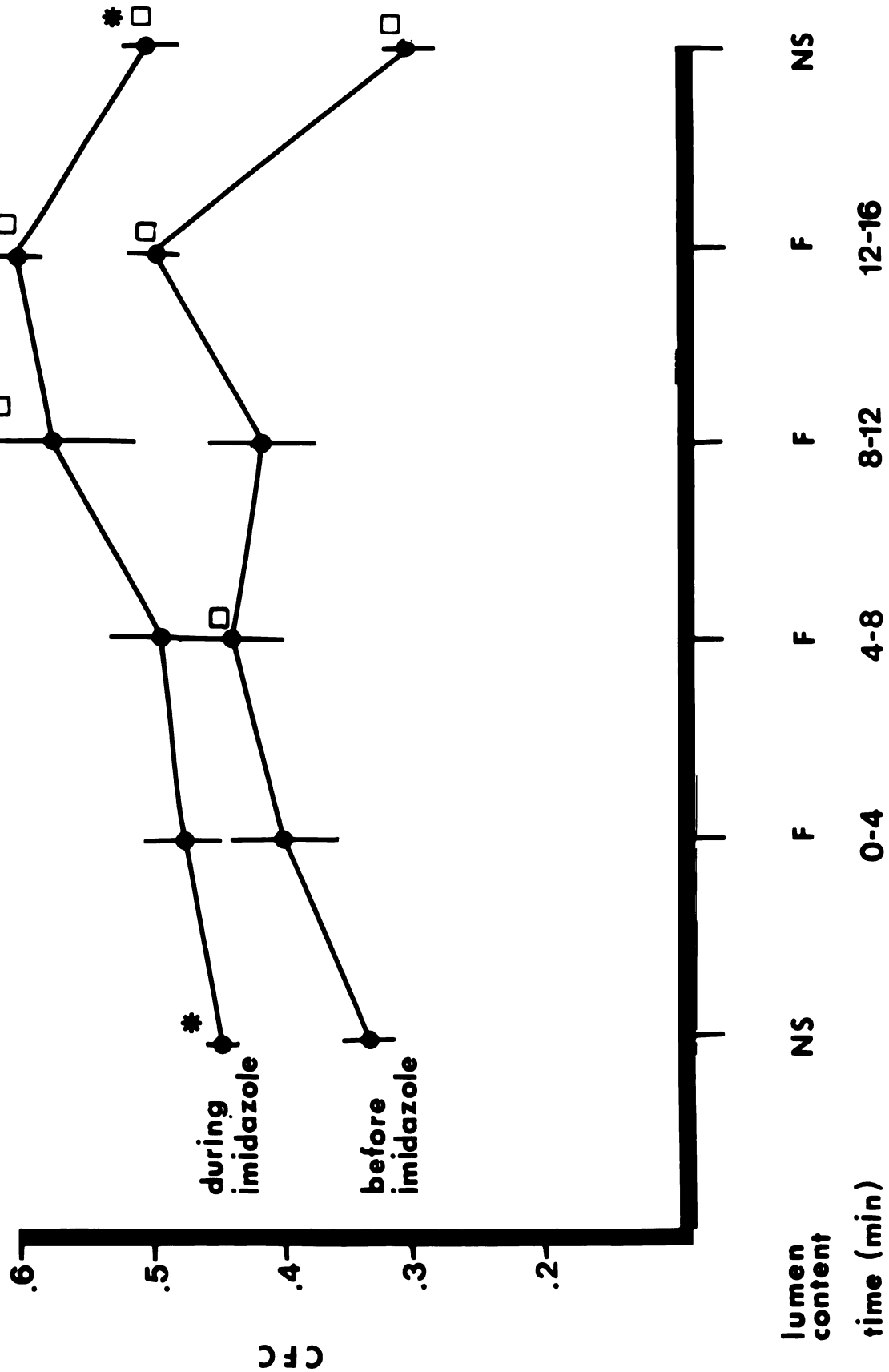
TABLE 5

Lumen Content	Before Imidazole	After Imidazole
Normal saline	-2.19 ±.92	-2.98 ±.86
Food	7.37 ±1.8	9.30 ±3.5
Net Absorption	9.60 ±1.4	12.3 ±3.2

	Before U-63557A	After U63557A
Normal Saline	-4.55 ±1.7	-1.45 ±1.9
Food	7.17 ±2.3	6.37 ±2.9
Net Absorption	11.7 ±2.6	7.64 ±3.3

Figure 15. Time course of changes in jejunal CFC during luminal placement of food before and during i.a. infusions of imidazole. CFC expressed as $ml \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot 100g^{-1}$. NS = normal saline, F = food. Squares $P < 0.05$ relative to NS, * $P < 0.05$ relative to the corresponding value before imidazole, n = 7.

Fig. 15

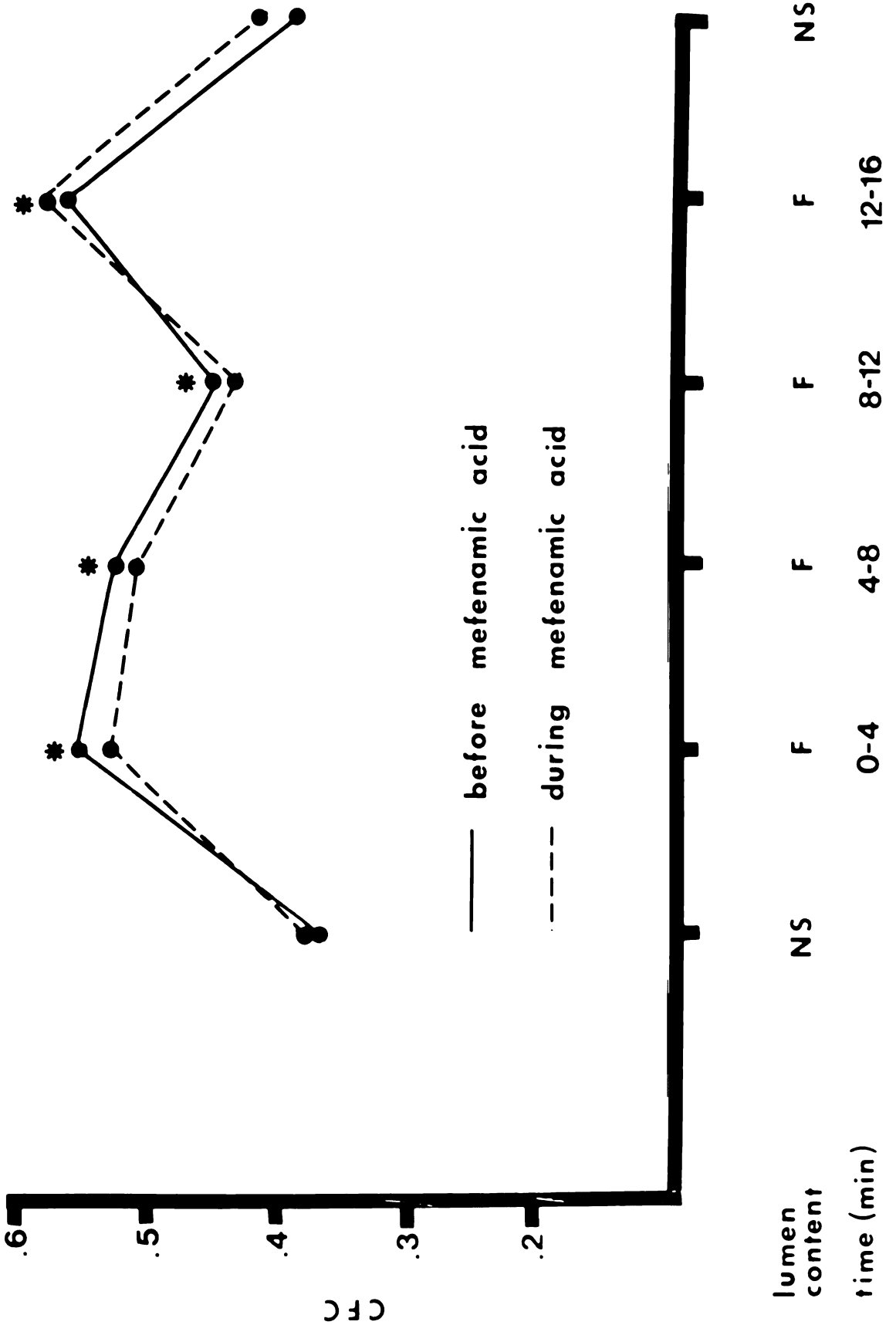

CFC
.6
.5
.4
.3
.2
during imidazole
before imidazole
lumen content
time (min)
NS
F
0-4
F
4-8
F
8-12
F
12-16
NS

significantly higher than that measured during normal saline placement. Furthermore, the CFC measured during the last 8 minutes of food placement during imidazole infusions were significantly greater than those measured before imidazole. This study indicates that endogenous TXA_2 acts to inhibit capillary exchange capacity at resting conditions as well as during digestion. Elevation of venous pressure had no significant affect on either the volume of fluid absorbed or motility before or during imidazole treatment.

Figure 16 shows the effect of mefenamic acid (cyclooxygenase inhibitor) on the jejunal CFC before food placement and 4, 8, 12, and 16 minutes following placement of food into the jejunal lumen. Before mefenamic acid and with saline in the lumen, CFC was 0.371 $\pm$ 0.01. During food placement, CFC rose to 0.558 $\pm$ 0.06, 0.524 $\pm$ 0.03, 0.453 $\pm$ 0.02, and 0.562 $\pm$ 0.01, 4, 8, 12, and 16 minutes following food placement, respectively. All of these values were significantly greater than the control value (0.371 $\pm$ 0.01). After mefenamic acid and with saline in the lumen, CFC was 0.375 $\pm$ 0.02 which was not significantly different from that observed before mefenamic acid (0.371 $\pm$ 0.01). During food placement, CFC rose to 0.533 $\pm$ 0.03, 0.517 $\pm$ 0.02, 0.445 $\pm$ 0.02, and 0.566 $\pm$ 0.04, 4, 8, 12, and 16 minutes following food placement, respectively. All these values were significantly greater than control (0.375 $\pm$ 0.02). Mefenamic acid treatment, therefore, had no

Figure 16. Time course of changes in jejunal CFC during luminal placement of food before and after i.v. infusion of mefenamic acid. CFC expressed as $ml \cdot min^{-1} \cdot mm\ Hg^{-1} \cdot 100g^{-1}$. NS = normal saline, F = food. * $P < 0.05$ relative to NS, n = 7.

Fig. 16


CFC
.6
.5
.4
.3
.2
before mefenamic acid
during mefenamic acid
lumen content
time (min)
NS
F
0-4
F
4-8
F
8-12
F
12-16
NS

significant effect on the jejunal CFC either before food placement or at any time during food placement. Elevation of venous pressure had no significant affect on either the volume of fluid absorbed or motility before or after mefenamic acid treatment.

DISCUSSION

The stimuli for the postprandial intestinal hyperemia are the products of food digestion such as fatty acids, sugars, and amino acids (37, 87). Many factors are involved in this response such as villus hyperosmolality (34), and gastrointestinal hormones (38, 52). Recently, locally released compounds have also been shown to be involved in this complex metabolic and vascular response to nutrient absorption. Chou and Siregar (39) have proposed that histamine plays an important role in the metabolic and vascular response to feeding. They found that tripelenamine, an H-1 histamine receptor antagonist, significantly attenuated the food-induced increases in intestinal blood flow and oxygen uptake. Another class of compounds which are present throughout the gastrointestinal tract that have been implicated in the postprandial intestinal hyperemia are the prostaglandins. Gallavan and Chou (63) have shown that inhibition of prostaglandin synthesis with indomethacin or mefenamic acid, significantly potentiated the food-induced increases in intestinal blood flow and oxygen uptake. Furthermore, there was a significant correlation between food-induced changes in blood flow and oxygen uptake before and after inhibition of prostaglandin synthesis. The authors concluded that endogenous intestinal prostaglandins serve

to limit the postprandial intestinal hyperemia and this may be secondary to prostaglandin-induced reductions in oxidative metabolism during nutrient absorption.

The postprandial intestinal hyperemia is confined mainly to the mucosal layer of the gut wall (36, 64, 141). The jejunal mucosa produces prostaglandins and the prostaglandins produced by the jejunal mucosa are prostaglandin I_2 and thromboxane A_2 (92, 93).

The purpose of the present study was to examine the contributions of endogenous intestinal prostaglandins to the postprandial intestinal hyperemia from the other direction, namely, to stimulate endogenous intestinal prostaglandin production with arachidonic acid. Also, in an attempt to identify the prostaglandins involved, the effect of selective inhibition of thromboxane synthesis on food-induced increases in jejunal blood flow and O_2 uptake was examined.

Arachidonic acid is the precursor of the bisenoic prostaglandins and has been shown to stimulate intestinal prostaglandin synthesis (3, 92, 115, 136). Since arachidonic acid has been reported to exert powerful vascular effects in the intestinal vascular bed (33, 46, 47), a dose response relationship of arachidonic acid on intestinal vascular resistance was determined. As shown in Figure 7, arachidonic acid exerts a biphasic effect on

jejunal vascular resistance in constant flow jejunal preparation. Low doses of arachidonic acid increase resistance while higher doses decrease resistance.

Most investigators have reported that arachidonic acid is a vasodilator in the intestinal vascular bed (33, 46, 47), but some have observed a biphasic response (33, 46, 82). In the gastric vascular bed (82) and in _in vitro_ studies using intestinal vascular smooth muscle strips (46), the same dose (82) or concentration (46) of arachidonic acid responsible for eliciting vasodilitation caused vasoconstriction if the amount of time that arachidonic acid was in contact with blood cells was increased. The authors (46, 82) suggested that the conversion from vasodilatory to vasoconstrictor action may be due to a preferential formation of platelet born vasoconstrictor thromboxanes. In order to test this possibility, the effects of i.a. infusions of arachidonic acid on jejunal vascular resistance were determined after the animals were pretreated with a single dose of aspirin (25 $mg \cdot kg^{-1}$, oral) 48 hours prior to the experiment. Aspirin blocks cyclooxygenase and platelets are 20-40 fold more sensitive to aspirin-induced inhibition of cyclooxygenase than other tissues (6). Furthermore, aspirin irreversibly acetylates platelet cyclooxygenase rendering them permanently incapable of prostaglandin production because they cannot synthesize protein (98). Nucleated cells, however, can completely replace their

acetylated cyclooxygenase in as little as 36 hours (81). On this basis, single low doses of aspirin have been used to preferentially inhibit the formation of cyclooxygenase products from platelets (81, 98).

As shown in Figure 8, increasing concentrations of arachidonic acid produced a dose dependent decrease in jejunal vascular resistance when the animals were pretreated with a single dose of aspirin 48 hours before the experiment (regression coefficient significant at $P < 0.05$). Furthermore, the increase in jejunal vascular resistance observed with arachidonic acid concentrations between 1.0 and 5.0 mg·ml blood^{-1} (Figure 7) was abolished. This indicates that the increase in jejunal vascular resistance observed with low concentrations of arachidonic acid (Figure 7) may have been due to the preferential formation of platelet prostaglandins, specifically thromboxane A_2.

The effects of i.a. infusions of arachidonic acid on jejunal vascular resistance in aspirin untreated or treated group (Figure 7 and Figure 8), may have been due to the products of arachidonic acid metabolism by cyclooxygenase, lipoxygenase, monooxygenase, or arachidonic acid per se. In order to determine if the vascular actions of arachidonic acid were due to only the products of cyclooxygenase metabolism, the effects of i.a. infusions of arachidonic acid on jejunal vascular resistance were determined after treatment with mefenamic acid, a selective

cyclooxygenase inhibitor. As shown in Figure 8, infusions of arachidonic acid at various concentrations had no effect on jejunal vascular resistance after mefenamic acid treatment (the regression coefficient is not significant at $P < 0.05$). This indicates that the effects of arachidonic acid on jejunal vascular resistance (Figure 7 and Figure 8) were due to the products of cyclooxygenase metabolism.

I.V. and i.a. infusions of either mefenamic acid or indomethacin (prostaglandin synthesis inhibitors) significantly potentiate the postprandial jejunal hyperemia (63). Therefore, we determined the effects of i.v. and i.a. infusions of arachidonic acid, a prostaglandin precursor, on the postprandial intestinal hyperemia in natural flow jejunal preparations. Table 2 shows that i.v. infusions of arachidonic acid (40 $\mu g \cdot kg^{-1} \cdot min^{-1}$) significantly attenuate the postprandial jejunal hyperemia. Furthermore, Table 1 shows that i.a. infusions of arachidonic acid (4-8 $\mu g \cdot ml\ blood^{-1}$) also significantly attenuated the postprandial jejunal hyperemia. The attenuation of the postprandial jejunal hyperemia by arachidonic acid (Table 1 and 2) suggest that endogenous intestinal prostaglandins serve to limit the vascular response to luminal flood placement, a hypothesis put forth by Gallavan and Chou who used cyclooxygenase inhibitors (63).

Because local i.a. infusions of indomethacin or mefenamic acid potentiated the postprandial intestinal hyperemia (63), Gallavan and Chou proposed that the effects of prostaglandin synthesis inhibition on the postprandial intestinal hyperemia were due to the inhibition of local jejunal prostaglandins and not due to an unidentified central mechanism or due to inhibition of prostaglandin synthesis by other somatic tissues. The present study supports that conclusion since local i.a. infusions of arachidonic acid attenuated the postprandial intestinal hyperemia (Table 1) as well as i.v. infusions (Table 2).

Both i.v. and i.a. infusions of arachidonic acid attenuate the postprandial jejunal hyperemia (Table 2 and 1). Unlike i.a. infusions of arachidonic acid, however, i.v. infusions significantly reduced jejunal blood flow when saline was in the lumen (Table 2). It is not clear from this study why this occurred. This effect may be due to unidentified central mechanisms or possibly vasoconstrictor prostaglandins produced by tissues other than the jejunum. For example, blood concentrations of arachidonic acid between 1.0 and 5.0 $\mu g \cdot ml\ blood^{-1}$ increase jejunal vascular resistance (Figure 7) and since the vasoconstrictor effect is abolished by single low doses of aspirin (Figure 8), the blood concentration of arachidonic acid reaching the intestine in the i.v. series might result in preferential production of platelet born vasoconstrictor prostaglandins.

The jejunal vascular and metabolic changes associated with luminal placement of digested food are confined mainly to the mucosal layer of the gut wall (36, 64, 141). Gallavan and Chou (63) have shown that i.a. administration of cyclooxygenase inhibitors potentiate the food-induced increases in jejunal blood flow and oxygen uptake. Conversly, i.a. infusions of arachidonic acid attenuate the postprandial intestinal hyperemia (Table 1). These data indicate that these effects may be due to changes in local intestinal prostagalndin production, more specifically, mucosal prostaglandins. In an attempt to test this possibility, the effects of luminal placement of arachidonic acid (0.65 mM) on the food-induced increases in intestinal blood flow and oxygen uptake in natural flow jejunal preparations was examined. Arachidonic acid is readily absorbed from the jejunal lumen (40) and would be expected to be available for cyclooxygenase metabolism only in the mucosal epithelial cells because fatty acids (like arachidonic acid) are transported through the lymphatics following chylomicron formation in the mucosal epithelium. As shown in Figure 4, luminal placement of arachidonic acid significantly attenuated the postprandial intestinal hyperemia. Likewise, Figure 9 shows that luminal placement of arachidonic acid attenuated the food-induced increases in jejunal oxygen uptake. Furthermore, the increases in jejunal blood flow and oxygen uptake following luminal placement of food are significantly correlated both before

and during arachidonic acid administration (Figure 10). The same correlations were also observed before and after prostaglandin synthesis inhibition by Gallavan and Chou (63). These authors (63) concluded that the effects of endogenous jejunal prostaglandins on the food-induced increases in jejunal blood flow may be the result of primary alterations in the food-induced increases in jejunal oxidative metabolism. The strong correlation between the food-induced increases in intestinal blood flow and oxygen uptake both before and during arachidonic acid administration (Figure 10) supports this hypothesis. It is also possible that the attenuation of the food-induced increases in jejunal blood flow by arachidonic acid were due to changes in mucosal prostaglandin production since luminal placement of arachidonic acid attenuated the food-induced increases in both intestinal blood flow and oxygen uptake.

Arachidonic acid attenuates the food-induced increases in intestinal oxygen uptake (Figure 9) as well as blood flow (Table 1, Table 2, and Figure 4). The attenuation of the food-induced increases in oxygen uptake might be secondary to the attenuation of the hyperemia. To test this possibility, the effects of mechanical alterations in intestinal blood flow on intestinal oxygen uptake were examined. Figure 11 shows that oxygen uptake remains unchanged over the blood flow range of 34-110 $ml \cdot min^{-1} 100g^{-1}$. Below 34 $ml \cdot min^{-1} \cdot 100g^{-1}$, oxygen uptake was flow

dependant. Other investigators have also shown this relationship in ileal preparations (88). Since the blood flow values in our preparations were above 34 $ml \cdot min^{-1} \cdot 100g^{-1}$, any alterations in intestinal oxygen uptake appear not to be the result of alterations in intestinal blood flow. In fact, the converse may be argued, that is, the attenuation of the food-induced increases in intestinal blood flow may be secondary to the attenuation of the food-induced increases in intestinal oxygen uptake.

The attenuation of the postprandial intestinal hyperemia by arachidonic acid (Figure 4, Table 1, and Table 2) as well as the attenuation of the food-induced increases in intestinal oxygen uptake (Figure 9) may have been due to the action of either prostaglandins or arachidonic acid <u>per se</u>. In order to assess this possibility, the effects of arachidonic acid on the food-induced increases in intestinal blood flow and oxygen uptake were determined after blocking cyclooxygenase with mefenamic acid. Table 3 shows that the attenuation of the food-induced increases in intestinal blood flow and oxygen uptake by intra-arterial infusions of arachidonic acid were abolished by mefenamic acid, a prostaglandin synthesis inhibitor. This indicates that the effects of arachidonic acid were the result of stimulation of prostaglandin synthesis. The use of mefenamic acid in this series also rules out the possible involvement of other arachidonic acid pathways since mefenamic acid only inhibits cyclooxygenase, the enzyme

responsible for production of bisenoic prostaglandins and prostanoids. More specifically, the results of this series of experiments rules out the involvement of the lipoxygenase or monooxygenase products in the attenuation of the metabolic and vascular responses to food placement induced by arachidonic acid.

The prostaglandins produced by the jejunal mucosa are prostaglandin I_2 and thromboxane A_2 (92, 93). Furthermore, thromboxane A_2 is only produced in the mucosal layer of the gut wall (93). Selective inhibition of thromboxane synthesis has been shown to inhibit the production of thromboxane A_2 and increase the production of prostaglandin I_2 by reorienting endoperoxide metabolism toward prostaglandin I_2 synthesis (20, 43, 105). Therefore, selective inhibitors of thromboxane synthesis were used to determine if a change in the thromboxane to prostacyclin production ratio would have an effect on either the food-induced increases in jejunal blood flow or oxygen uptake.

Imidazole has been shown to be one of the most efficacious inhibitors of thromboxane synthesis *in vivo* (44) and *in vitro* (43, 57, 105) and was one of the two thromboxane synthesis inhibitiors used in this study. As shown in Figure 12, i.a. infusions of imidazole had no effect on the food-induced increases in jejunal blood flow but significantly potentiated the food-induced increases in

jejunal oxygen uptake (Figure 13). This means that the increased oxygen uptake by imidazole was met by increases in oxygen extraction and not blood flow.

Furthermore, the slope of the correlation between food-induced increases in intestinal blood flow and oxygen uptake of the treated group (imidazole) is significantly less than that of the untreated group (control) (Figure 14). In Figure 14, the data are expressed as percent change from control but the same correlation also holds if absolute flow and oxygen uptake values are used. More specifically, the equation for food-induced increases in oxygen uptake (X) vs. food-induced increases in blood flow (y) was $y = 67.3 x + 7.0$, $r = 0.70$ (linear regression analysis) and after imidazole the equation was $y = 20.9 x + 1.5$, $R = 0.91$ (linear regression anaylysis). The slopes are significantly different at $P < 0.05$. In previous studies using total prostaglandin synthesis inhibition (mefenamic acid) (63) or total prostaglandin synthesis stimulation (arachidonic acid) (Figure 10), the correlations between flow and oxygen uptake of the treated and untreated groups share the same regression line, i.e. for a given increase in oxygen uptake, the corresponding increase in blood flow in the treated and untreated groups are the same. This is different from that shown in Figure 14, i.e. for a given increase in oxygen uptake, the corresponding increase in blood flow during imidazole infusions is significantly less than that observed before

the infusion (control, Figure 14). The difference may be that imidazole enhances oxygen uptake by enhancing intestinal metabolism during nutrient absorption without affecting the intestinal hyperemia.

In order to determine whether imidazole increases glucose absorption, thereby increasing intestinal metabolism and oxygen uptake, the effect of imidazole on glucose absorption was studied. As shown in Table 5, glucose absorption during food placement was unaffected by imidazole treatment. This would suggest that the increase in metabolic rate that accompanied active glucose absorption is not affected by imidazole. Furthermore, imidazole per se did not alter resting intestinal oxygen uptake (Figure 13). It appears that the potentiation of the food-induced increases in intestinal oxygen uptake by imidazole is not the result of enhanced glucose absorption.

The effects of imidazole on the food-induced increases in blood flow (Figure 12), oxygen uptake (Figure 13), and glucose absorption (Table 5) are believed to be due to inhibition of thromboxane synthesis. To further strengthen this argument, the effects of Sodium 5- (3'-Pyridinylmethyl) Benzofuran - 2 - Carboxylate (U-63557A) on food-induced increases in blood flow, oxygen uptake, and glucose absorption were studied. U-63557A is a selective inhibitor of thromboxane synthesis and does not contain an imidazole moity in its molecular structure (139). Table 4 shows that U-63557A had no effect on the food-induced

increases in intestinal blood flow, but like imidazole (Figure 13), significantly potentiated the food-induced increases in intestinal oxygen uptake. Furthermore, U-63557A had no significant effect on intestinal glucose absorption (Table 5). The glucose absorption data shown in Table 5 have large standard errors. The reason for this diversity is unclear. All glucose absorption data were normalized to 100g tissue weight, but it seems possible that the absorptive surface area may be different for intestinal segments of the same weight. If this were the case, glucose absorption rates may also be different, and this may account for the large standard errors (Table 5). Imidazole appeared to enhance glucose absorption, while U-63557A decreased glucose absorption. Therefore, we believe that thromboxane synthesis inhibition has no significant effect on intestinal glucose absorption. Since we were able to reproduce the findings from the imidazole studies with a different thromboxane synthesis inhibitor, it seems very possible that intestinal thromboxanes are involved in regulating oxygen uptake during nutrient absorption.

It has been shown that the increase in intestinal oxygen uptake during nutrient absorption is not necessarily accompanied by an increase in blood flow (122). The increased oxygen uptake in this situation was primarily met by an increase in tissue oxygen extraction. Although the underlying mechanisms are unclear, enhanced glucose absorption has been implicated to be a possible mechanism

whereby oxygen uptake increases via enhanced oxygen extraction and not blood flow (122). However, our data indicate that the rate of intestinal glucose absorption is unaffected by thromboxane synthesis inhibitors (Table 5). Although glucose absorption is not affected by imidazole or U-63557A, it may be that the potentiation of the food induced increase in oxygen uptake by these two inhibitors were the result of increased metabolism due to enhanced peptide, animo acid, fat or electrolyte absorption. This possibility was not examined in this study.

Luminal placement of food solutions into the small intestine increase intestinal capillary exchange capacity as indexed by the capillary filtration coefficient (122), the capillary permeability-surface area product from Rb clearance (122), and by the osmotic reflection coefficient (69). The increase in the intestinal PS product is believed to be due to capillary recruitment which enhances the delivery of oxygen to the mucosal cells during the metabolic stress of nutrient absorption (122). In order to assess whether thromboxanes would increase jejunal capillary exchange capacity, the jejunal capillary filtration coefficient was determined before and during luminal food placement and the same procedures repeated following imidazole treatment.

Figures 15 and 16 clearly show that luminal placement of a digested food solution into the jejunum increases the capillary filtration coefficient. Furthermore, Figure 15

shows that imidazole enhanced the jejunal capillary filtration coefficient both before and during luminal food placement. Imidazole inhibits the production of vasoconstrictor thromboxane and increases production of vasodilator prostaglandin I_2 (43, 44, 105). If this were to occur at the level of the precapillary sphincters, the logical consequence would be capillary recruitment and an increase in the capillary filtration coefficient. An increase in capillary recruitment by imidazole during the metabolic stress of nutrient absorption could lead to an enhanced flux of oxygen into the metabolically active intestinal parenchamal cells by decreasing the capillary-to-cell diffusion distance. Before food placement, however, an increase in the jejunal capillary exchange capacity would not result in enhanced oxygen flux. Oxygen delivery may still be enhanced but a large gradient for oxygen diffusion is not present in the nonabsorbing intestine. Indeed, Figure 15 shows that imidazole enhanced jejunal capillary exchange capacity before the metabolic stress of nutrient absoprtion but imidazole had no effect on resting oxygen uptake (Figure 13).

Mefenamic acid inhibits all prostaglandin production by preventing endoperoxide formation. Mefenamic acid also potentiates the food-induced increases in intestinal blood flow and oxygen uptake (63). In our studies, mefenamic acid did not alter the time dependant changes in jejunal CFC when food was placed into the lumen (Figure 16). This

may be because only the relative amounts of prostaglandin I_2 and thromboxane were altered and not their ratios. The potentiation of the food-induced increases in jejunal oxygen uptake by mefenamic acid (63) may be due to direct actions on tissue metabolism and not alterations in capillary exchange capacity.

Selective inhibition of intestinal thromboxane production increases oxygen uptake during nutrient absorption, and this is accomplished by an increase in oxygen extraction and not blood flow. Furthermore, this appears not to be due to enhanced mucosal metabolism associated with enhanced glucose absorption. Inhibition of thromboxane synthesis also enhances intestinal capillary exchange capacity (CFC) before and during nutrient absorption. It may be that the potentiation of the food-induced increase in intestinal oxygen uptake associated with inhibition of thromboxane synthesis is the result of concommitant microcirculatory adjustments resulting in increases in the capillary-to-cell flux of oxygen in the mucosa during the metabolic stress of nutrient absorption.

In conclusion, endogenous intestinal prostaglandins serve to limit the postprandial intestinal hyperemia. Endogenous prostaglandins appear to act as a "break" in controlling intestinal blood flow during nutrient

absorption. Furthermore, the prostaglandins involved may be those produced by the mucosa and their effects may be due to alterations in the metabolic or microcirculatory adjustments associated with nutrient absorption.

CONCLUSIONS

1. Intra-arterial infusions of arachidonic acid produce a biphasic effect on intestinal vascular resistance: low doses increase whereas higher doses decrease resistance. These effects are due to prostaglandin production and the vasoconstrictor effects may be due to platelet born thromboxanes.

2. Arachidonic acid significantly attenuates the food-induced increases in jejunal blood flow when administered i.a., i.v., or placed into the jejunal lumen. Luminal placement of arachidonic acid attenuates the food-induced increases in intestinal oxygen uptake. These effects are due to prostaglandin synthesis and not arachidonic acid *per se*. The prostaglandins involved are locally produced and may be those produced by the mucosa.

3. Mechanical alterations of jejunal blood flow have no effect on jejunal oxygen uptake. This indicates that the attenuation of the food-induced increases in jejunal oxygen uptake by arachidonic acid was not the result of primary changes in jejunal blood flow.

4. Food-induced changes in jejunal oxygen uptake and blood flow are significantly correlated before (control group) and during arachidonic acid administration (treated group). Furthermore, the control and treated groups share the same regression line.

5. Thromboxane synthesis inhibitors (imidazole and U-63557A) have no effect on food induced increases in jejunal blood flow but significantly potentiate food-induced increases in jejunal oxygen uptake. Thromboxane synthesis inhibitors have no effect on the rate of jejunal glucose absorption. This indicates that the potentiation of the food-induced increases in jejunal oxygen uptake by thromboxane synthesis inhibitors is not due to enhanced metabolism associated with enhanced glucose absorption.

6. Food-induced changes in jejunal oxygen uptake and blood flow are significantly correlated before (control group) and after thromboxane synthesis inhibitors (treated group). Furthermore, the regression line of the treated group is significantly different from the control group.

7. Luminal placement of food significantly increases the jejunal capillary filtration coefficient (CFC). Imidazole significantly increased jejunal CFC before and during food placement. Mefenamic acid, a cyclooxygenase inhibitor, had no effect on jejunal CFC before or during food placement.

BIBLIOGRAPHY

BIBLIOGRAPHY

1. Ambache, N., H.C. Brummer and J.G. Rose. Thin layer chromatography of spasmogenic unsaturated hydroxy acids from various tissues. J. Physiol (Lon.) 185: 77-78 P, 1966.

2. Anggard, E. and S. Bergstrom. Biological effects of an unsaturated Trihydroxy acid (PGF_2) from normal swine lung. Acta. Physiol. Scand. 58: 1-12, 1963.

3. Anggard E. and B. Samuelsson. Biosynthesis of prostaglandins from arachidonic acid in guinea pig lung. J Biol Chem 240: 3518-3521, 1965.

4. Armstrong, J.M., N. Lattimer, S. Moncada and J.R. Vane. Comparison of the vasodepressor effects of prostacyclin and 6-oxoprostaglandin F_1 with those of prostaglandin E_2 in rats and rabbits. Br. J. Pharmacol. 62: 105-129, 1978.

5. Balent, G.A., Z.F. Riss, T. Varkonyi, T. Whittmann and V. Vargo. Effects of prostaglandin E_2 and F_2 on the absorption and portal transport of sugar on the local intestine circulation. Prostaglandins 18: 265-268, 1979.

6. Baenziger, N.L., P.R. Beckerer, and P.W. Majerus. Characteristics of prostaglandin synthesis in cultured human arterial smooth muscle cells, venous endothelial cells, and skin fibroblasts. Cell 16: 967-974, 1979.

7. Bartho, L. Adrenergic responses of the guinea pig ileum: inhibition by prostaglandins and potentiation by non-steroid anti-inflammatory drugs. Am. J. Physiol. 235: 238-247, 1978.

8. Bell, R. L. and P. W. Majerus. Thrombin-induced hydrolysis of phosphatidylinositol in human platelets. J Biol Chem 255: 1790-1792, 1980.

9. Bennett, A., K.G. Eley and G.B. Scholes. Effects of prostaglandins E_1 and E_2 on human, guinea pig, and rat isolated small intestine. Br. J. Pharmacol. 34: 630-638, 1968.

10. Bennett, A., K.G. Eley and G.B. Scholes. Effects of prostaglandins E_1 and E_2 on intestinal motility in the guinea pig and rat. Br. J. Pharmacol. 34: 639-647, 1968.

11. Bergstrom, S.H., H. Danielsson and B. Samuelsson. The enzymatic formation of prostaglandin F_2 from arachidonic acid. Biochim Biophys Acta 90:207, 1964.

12. Bergstrom, S., R. Eliasson, U.S. v. Euler, and J. Sjovall. Some biological effects of two crystalline prostaglandin factors. Acta. Physiol. Scand. 45: 133-144, 1959.

13. Bergstrom, S. and J. Sjovall. The isolation of prostaglandin. Acta Chem Scand 11: 1086, 1957.

14. Bergstrom, S. and J. Sjovall. The isolation of prostaglandin F from sheep prostate glands. Acta Chem Scand 14: 1701, 1960.

15. Beubler, E. and H. Juan. PGE release, blood flow and transmucosal water movement after mechanical stimulation of the rat jejunal mucosa. Naun Schmeid Arch. Pharmacol. 305: 91-95, 1978.

16. Biber, B., O. Lundgren and J. Svanoik. Studies on the intestinal vasodilation observed after mechanical stimulation of the mucosa of the gut. Acta. Physiol. Scand. 82: 177-190, 1971.

17. Biber, B. Vasodilator mechanisms in the small intestine. Acta Physiol. Scand. Suppl. 401, 1973.

18. Bill, A. Effects of indomethacin on regional blood flow in conscious rabbits - a microsphere study. Acta Physiol. Scand. 105: 437-442, 1979.

19. Bills, T.K., J.B. Smith and M.J. Silver. Selective release of arachidonic acid from the phospholipids of human platelets in response to thrombin. J Clin Invest 60: 1-6, 1977.

20. Blackwell, G.J., R.J. Flower, N. Russel-Smith, J.A. Salmon, R.B. Thorogood and J.R. Vane. 1-n-Butylimidazole: A potent and selective inhibitor of thromboxane synthetase. Proceedings of the B.P.S. p. 435, 1978.

21. Bohlen, H.G. Intestinal mucosal oxygenation influences absorptive hyperemia. Am. J. Physiol. 239 (Heart Circ. Physiol. 8): H489-H493, 1980b.

22. Bohlen, H.G. Intestinal tissue PO_2 and microvascular responses during glucose exposure. Am. J. Physiol. 238 (Heart Circ. Physiol. 7): H164-H171, 1980a.

23. Bond, J.H., R.A. Prentiss and M.D. Levitt. The effects of feeding on blood flow to the stomach, small bowel, and colon of the conscious dog. J. Lab Clin. Med. 93: 594-599, 1979.

24. Borgstrom, B., A. Dahlquist, G. Lundh and J. Sjovall. Studies of intestinal digestion and absorption in the human. J. Clin. Invest. 36: 1521-1536, 1957.

25. Botting, J.H. The effect of indomethacin on the release of prostaglandin E_2 and acetylcholine from guinea pig isolated ileum at rest and during field stimulation. Br. J. Pharmacol. 50: 119-124, 1974.

26. Brandt, J.L., L. Castleman, H.D. Ruskin, J.J. Greenwald and J. Kelly. The effect of oral protein and glucose feeding on splanchnic blood flow and oxygen utilization in normal and cirrhotic subjects. J. Clin. Invest. 34: 1017-1025, 1955.

27. Brodie, T.G., W.C. Cullis and W.D. Halliburton. The gaseous metabolism of the small intestine. II. The gaseous exchanges during the absorption of Witte's peptone. J. Physiol. 40: 173-189, 1910.

28. Broekman, M.J., J.W. Ward and A.J. Marcus. Phosopholipid metabolism in stimulated human platelets. Changes in phosphatidylinositol, phosphatidic acid, and lysophospholipids. J Clin Invest 66: 275-283, 1980.

29. Bukhave, K. and J. Rask-Madsen. Saturation kinetics applied to *in vitro* effects of low prostaglandin E_2 and F_2 concentrations on ion transport across human jejunal mucosa. Gastroent. 78: 32-42, 1980.

30. Burns, G.P. and W.G. Schenk. Effect of digestion and exercise on intestinal blood flow and cardiac output. Arch. Surg. 98: 790-794, 1969.

31. Burns, G.P. and W.G. Schenk. Intestinal blood flow in the conscious dog. Surg. Forum 18: 313-315, 1967.

32. Castenfors, H., H. Elliasch and E. Hultman. Effects of ingestion of hyperosmotic glucose solution on the splanchnic circulation in normal subjects and in partially gastrectomized patients reacting with circulatory collapse. Scan. J. Clin. Lab.Invest. 13: 512-524, 1961.

33. Chapnick, B.M., L.P. Feigen, A.L. Hyman and P.J. Kadowitz. Differential effects of prostaglandins in the mesenteric vascular bed. Am. J. Physiol. 235: H326-H332, 1978.

34. Chou, C.C., T.D. Burns, C.P. Hsiehm and J.M. Dabney. Mechanisms of local vasodilation with hypertonic glucose in the jejunum. Surgery 71: 380-387, 1972.

35. Chou, C.C., C.P. Hsieh, T.D. Burns and J.M. Dabney. Effects of lumen pH and osmolarity on duodenal blood flow and motility. Gastoenterology 60: 648, 1971.

36. Chou, C.C., C.P. Hsieh, Y.M. Yu, P. Kvietys, L.C. Yu, R. Pittman and J.M. Dabney. Localization of mesenteric hyperemia during digestion in dogs. Am. J. Physiol. 230: 583-589, 1976.

37. Chou, C.C., P. Kvietys, J. Post and S.P. Sit. Constituents of chyme responsible for postprandial intestinal hyperemia. Am. J. Physiol. 235 (Heart Circ. Physiol. 4): H667-H682, 1978.

38. Chou, C.C., M.J. Mangino and D.R. Sawmiller. Gastrointestinal hormones and intestinal blood flow. In: Physiology of the Intestinal Circulation, edited by A.P. Shepherd and D.N. Granger. New York, New York: Raven Press, 1984, p. 121-130.

39. Chou, C.C. and H. Siregar. Role of histamine H_1- and H_2-receptors in postprandial intestinal hyperemia. Am. J. Physiol. 243 (Gastrointest. Liver Physiol. 6): G248-G252, 1982.

40. Chow, S.L. and D. Hollander. Arachidonic acid intestinal absorption: mechanism of transport and influence of luminal factors on absorption in vitro. Lipids 13: 768-776, 1978.

41. Dagenais, G.R., A. Oriol and M. McGregor. Hemodynavic effects of carbohydrate and protein meals in man: rest and exercise. J. Appl. Physiol. 21: 1157-1162, 1966.

42. Dajani, E.Z., R.E. Bertermann, E., A.W. Roge, F.L. Schweingruber and E.M. Woods. Canine gastrointestinal motility effects of PGE_2 in vivo. Am. J. Physiol. 237: 16-24, 1979.

43. DeFreyn, G. A TXA_2 synthetase inhibitor reorients endoperoxide metabolism in whole blood towards PGI_2 and PGE_2. Thromboxane Res. 26: 389-400, 1982.

44. Dunham, B.M., G.A. Grindlinger, T. Utsonomiya, M.M. Krausz, H.B. Hechtman and D. Shepro. Role of prostaglandins in end-expiratory pressure-induced negative inotropism. Am. J. Physiol. 241: H783-H788, 1981.

45. Dupont, J., S. Meydani, G.L. Case, R.V. Phillips and L.D. Lewis. Prostaglandins and their metabolites in the gastrointestinal tract of Yucatan miniature swine. Am. J. Clin. Nutr. 34: 2048-2053, 1981.

46. Dusting, G.J., S. Moncada, K.M. Mullane and J.R. Vane. Biotransformation of arachidonic acid in the circulation of the dog. Br. J. Pharmacol. 63: 359P, 1978.

47. Dusting, G.J., S. Moncada and J.R. Vane. Vascular actions of arachadonic acid and its metabolites in perfused mesenteric and femoral beds of the dog. Eur. J. Pharmacol. 49: 65-72, 1978.

48. Eliasson, R. Studies on prostaglandins -- occurence, formation, and biological actions. Acta Physiol Scand 46:1 (suppl 158). 1959.

49. Euler, U.S. von. Uber die spezifische blutdrecksenkende substanz des menslicken prostataund samenblasensektetes. Klin. Wschr. 14: 1182-1183, 1935.

50. Famaey, J.P., J. Fontaine, I. Seaman and J. Reuse. A possible role of prostaglandins in guinea pig isolated ileum contractions to serotonin. Prostaglandins 14: 119-124, 1977.

51. Fara, J.W., K.H. Barth, R.I. White and T.E. Bynum. Mesenteric vascular effects of prostaglandin F_2 and B_2. Radiol. 133: 317-320, 1979.

52. Fara, J.W., E.H. Rubinstein and R.R. Sonnenshein. Intestinal hormones in the mesenteric vasodilation after intraduodenal agents. Am. J. Physiol. 223: 1058-1067, 1972.

53. Fara, J.W., E.H. Rubinstein and R.R. Sonnenshein. Visceral and behavioral responses to intraduodenal fat. Science 166: 110-111, 1969.

54. Feigen, L. and B. Chapnick. Evidence for separate PDG_2 and PGF_2 receptors in the canine mesenteric vascular bed. Adv. Prost. Thromb. Res. 6: 385-387, 1980.

55. Ferreira, S.H., A.G. Herman and J.R. Vane. Prostaglandin production by rabbit isolated jejunum and its relationship to the inherent tone of the preparation. Br. J. Pharmacol. 56: 469-477, 1976.

56. Ferreira, S.H. and J.R. Vane. Prostaglandins: Their disappearance from and release into the circulation. Nature 216: 868-873, 1967.

57. Fitzgerald, G.A., and J.A. Oates. Selective and nonselective inhibition of thromboxane formation. Clin. Pharmacol. Ther. 35:633-640, 1984.

58. Fondacaro, J.D., K.M. Walus, M. Schwaiger and E.D. Jacobson. Vasodilation of the normal and ischemic canine mesenteric circulation. Gastroent. 80: 1542-1549, 1981.

59. Fordtran, J.S., and T.W. Locklear. Ionic constituents and osmolality of gastric and small-intestinal fluids after eating. Am. J. Dig. Dis. 11: 503-521, 1966.

60. Frame, M.H. and I.H.M. Main. Effects of Arachidonic acid on rat gastric acid secretion in response to different secretagogues: Inhibition of these effects by indomethacin. Br. J. Pharmacol. 69: 171-178, 1980.

61. Fronek, K. and A. Fronek. Combined effect of exercise and digestion on hemodynamics in conscious dogs. Am. J. Physiol. 218: 555-559, 1970.

62. Fronek, K. and L.H. Stahlgren. Systemic and regional hemodynamic changes during food intake and digestion in nonanesthetized dogs. Circ. Res. 23: 687-692, 1968.

63. Gallavan, R.H., Jr. and C.C. Chou. Prostaglandin synthesis inhibition and postprandial intestinal hyperemia. Am. J. Physiol. 242 (Gastrointest. Liver Physiol. 5): G140-G146, 1982.

64. Gallavan, R.H., Jr., C.C. Chou, P.R. Kvietys and S.P. Sit. Regional blood flow during digestion in the conscious dog. Am. J. Physiol. 238: H220-H225, 1980.

65. Gallavan, R.H., Jr., and E.D. Jacobson. Prostaglandins and the splanchnic circulation. Proc. Soc. Exp. Biol. Med. 170: 391-397, 1982.

66. Gershon, M.D. and S.M. Erde. The nervous system of the gut. Gastroenterology 80: 1571-1594, 1981.

67. Goldblatt, A.W. A depressor substance in seminal fluid. J. Soc. Chem. Ind. (Lond) 52: 1056, 1933.

68. Granger, D.N., P.R. Kvietys and M.A. Taylor. Role of exchange vessels in the regulation of intestinal oxygenation. Am. J. Physiol. 242: G570-G574, 1982.

69. Granger, D.N., M.A. Perry, P.R. Kvietys, and A.E. Taylor. Permeability of intestinal capillaries: Efect of fat absorption and gastrointestinal hormones. Am. J. Physiol. 242: G194-G202, 1982.

70. Granger, D.N., J.S. Scackelford and A.E. Taylor. PGE_1-induced intestinal secretion - mechanism of enhanced transmucosal protein efflux. Am. J. Physiol. 236: E788-E796, 1979.

71. Greenberg, S.P., J. Kadowitz, J.P. Long and W.R. Wilson. Studies on the nature of a prostaglandin receptor in canine and rabbit vascular smooth muscle. Circ. Res. 39: 66-76, 1976.

72. Grollman, A. Physiological variations in the cardiac output of man. III. The effect of the ingestion of food on the cardiac output, pulse rate, blood pressure and oxygen consumption of man. Am. J. Physiol. 89: 366-370, 1929.

73. Hamberg, M. and B. Samuelsson. Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. Proc. Natl. Acad. Sci. USA 70: 899, 1973.

74. Hamberg, M., Svensson, J. and B. Samuelsson. Thromboxanes: A new group of biologically active compounds derived from prostaglandin endoperoxides. Proc. Natl. Acad Sci. USA 72: 2994, 1975.

75. Hatano, Y., J.D. Kohli, L.I. Goldberg and J. Freid. Interactions between different prostaglandins and other relaxing agents on isolated vascular smooth muscle. Adv. Prost. Thromb. Res. 7: 683-686, 1980.

76. Hawkins, H., J. Smith, K. Nicoloau and T. Eling. Studies of the mechanisms involved in the fate of prostacyclin and 6-keto-PGF_1 in the pulmonary circulation. Prostaglandins 16: 871-884, 1978.

77. Herrick, J. F., H. E. Essex, R. C. Mann and E.J. Baldes. The effect of digestion on blood flow in certain blood vessels of the dog. Am. J. Physiol. 108: 621-268, 1934.

78. Hopkinson, B. R. and W. G. Schenk. The electromagnetic measurement of liver blood flow and cardiac output in conscious dogs during feeding and exercise. Surgery 63" 970-975, 1968.

79. Horton, E. W. Action of PGE_1 on tissues which respond to bradykinin. Nature 200: 892-893, 1963.

80. Hsieh, C. P., J. M. Dabney, W. T. Chen, and C. C. Chou. Effect of lumen acidity and osmolarity on duodenal bloodflow and motility. Physiologist 13: 227, 1970.

81. Jaffe, E.A., and B.B. Weksler. Recovery of endothelial cell prostacylin production after inhibition of law doses of aspirin. J. Clin. Invest. 63: 532-535, 1979.

82. Kauffman, G. L., Jr., and J. R. Whittle. Gastric vascular actions of prostanoids and the dual effect of arachidonic acid. Am. J.Physiol. (Gastrointest. Liver Physiol. 5): G582-G587, 1982.

83. Khairallah, P. A., I. H. Page and R. K. Tucker. Some properties of prostaglandin E_1 action on muscle. Arch. Int. Pharm. 169: 328-341, 1967.

84. Kimberg, D. V., M. Field, J. Johnson, A. Henderson and E. Gershow. Stimulation of intestinal mucosal adenyl cyclase by cholera endotoxin and prostaglandins. J. Clin. Inves. 50: 1218-1230, 1971.

85. Knapp, H. R., O. Oelz, B. J. Sweetman and J. A. Oates. Synthesis and metabolism of prostaglandins E_2, F_2 , and D^2 by the rat gastrointestinal tract. Stimulation by a hypertonic environment in vitro. Prostaglandins 15: 751-575, 1978.

86. Kurzrok, R. and C. C. Lieb. Biochemical studies of human semen: II. The action of semen on the human uterus. Proc. Soc. Exp. Biol. Med. 28: 268, 1930.

87. Kvietys, P., R. Gallavan, R. Nyhof and C. C. Chou. Contribution of bile to the prostprandial intestinal hyperemia. Am. J. Physiol. 238: G284-G288, 1980.

88. Kvietys, P. R., and D. N. Granger. Relation between intestinal blood flow and oxygen uptake. Am. J. Physiol. 242: G202-G208, 1982.

89. Kvietys, P. R., D. N. Granger, N. A. Mortillaro and A. E. Taylor. Effect of atropine on fatty acid induced changes in blood flow, oxygen consumption, and water transport. Physiologist 22: 74, 1979.

90. Kvietys, P. R., M. A. Perry and D. N. Granger. Intestinal capillary exchange capacity and oxygen delivery-to-demand ratio. Am. J. Physiol. 245: G635-G640, 1983.

91. Lackeman, R. and L. Herman. Release of prostaglandin like material by various agonists from guinea pig lung and intestine. Arch. Int. Pharm. 236: 307-309, 1978.

92. LeDuc, L. E. and P. Needleman. Prostaglandin synthesis by dog gastrointestinal tract. Adv. Prost. Thromb.; Res. 8: 1515-1517, 1980.

93. LeDuc, L. E. and P. Needleman. Regional localization of prostacyclin and thromboxane synthesis in dog stomach and intestinal tract. J. Pharm. Exp. Ther. 211: 181-188, 1979.

94. Lunderquist, A. Angiographic changes during digestion. Am. J. Roetgenol. 107: 191-197, 1969.

95. Main, I. H. M. and B. J. R. Whittle. The effects of E and A prostaglandins on gastric mucosal blood flow and acid secretion in the rat. Br. J. Pharmacol. 49: 428-436, 1973.

96. Malik, K. U., P. Ryan and J. C. McGiff. Modification by prostaglandins E^1 and E^2, indomethacin and arachadonic acid of the vasoconstrictor responses of the isolated perfused rabbit and rat mesenteric arteries to adrenergic blockade. Circ. Res. 39: 163-168, 1976.

97. Manku, M. S., D. F. Horrobin, S. C. Cunnane, A. I. Ally, M. Karmazyn, R. A. Karmali, R. O. Morgan, K. C. Nicolaou and W. E. Barnette. Prostaglandins E^1 and E^2 and I^2: Evidence for three distinct actions in vascular smooth muscle. Biochem. Biophys. Res. Comm. 83: 295-299, 1978.

98. Marcus, A. J. The role of prostaglandins in platelet function. In: Progress in Hemotology, ed., E.B. Brown. New York: Grune and Stratton, Vol. 2, pp. 147-171, 1979.

99. Marcus, A. J., H. L. Ullman and L. B. Safier. Lipid composition of subcellular particles of human blood platelets. J. Lipid Res. 10: 108-117, 1969.

100. Matuchansky, C. and J. J. Brenier. Effects of PGE^1 on unidirectional movement of water and electrolytes across jejunal mucosa in man. Gut 12: 854-855, 1971.

101. Matuchansky, C. and J. J. Brenier. Effects of prostaglandin E^1 on jejunal absorption in man. Gastroent. 64: 1111-1118, 1973.

102. Matuchansky, C., J. Y. Mary and J. J. Brenier. Effects de la prostaglandin E^1 sur l'absorption du glucose et les mouvements transintestinaux de l'eau et des electrolytes dans le jejunum humain. Biol. Gastroent 5: 636C, 1972.

103. Mikkelessen, E. and K. E. Andersson. Contractile effects of prostaglandin F^2 on isolated human peripheral arteries and veins. Acta. Pharmacol Et Toxicol 43: 398-404, 1978.

104. Miy, B. F., W. C. Wu and G. E. Whalen. The effect of prostaglandin E^2 on net jejunal transport and mean transit time. Gastorent 66: 747-750, 1973.

105. Moncada, S., S. Bunting, K. Mullane, P. Thorogood, and J. R. Vane. Imidazole: A selective inhibitor of thromboxane synthetase. Prostaglandins 13: 611-618, 1977.

106. Norryd, C., H. Denker, A. Lunderquist, T. Olin and U. Tylen. Superior mesenteric blood flow during digestion in man. Acta Chir. Scand. 141: 197-202, 1975.

107. Nowak, J. and A. Wennonalm. Influence of indomethacin and of prostaglandin E^1 on total and regional blood flow in man. Acta. Physiol. Scand. 102: 484-491, 1978.

108. Nyhof, R. A. The role of mucosal nerves in the nutrient-induced intestinal hyperemia. Doctoral Dissertation, Michigan State University, 1981.

109. Nyhof, R. A. and C. C. Chou. Evidence against local neural mechanisms for intestinal postprandial hyperemia. Am. J. Physiol. 245: H437-H446, 1983.

110. Pawlik, W., A. P. Shepherd and E. D. Joacobson. Effects of vasoactive agents on intestinal oxygen consumption and blood flow in dogs. J. Clin. Inv. 56: 484-490, 1975.

111. Pierce, N. F., C. C. J. Carpenter, H. L. Elliott and W. B. Grennough. Effects of prostaglandin, theophylline and cholera endotoxin upon transmucosal water and electrolyte movement in the canine jejunum. Gastroent 60: 22-32, 1971.

112. Rask-Madsen, J. and K. Bukhave. Saturation kinetics applied to the inhibition by PGE^2 of ion transport in the isolated human jejunum. Adv. Prost. Thromb. Res. 8: 1595-1601, 1980.

113. Renninger, E. J. and S. Nutik. Determination of cardiac output following a meal in unanesthetized dogs. Fed. Proc. 19: 118, 1960.

114. Renninger, E.J. and L. A. Sapirstein. Effect of digestion on distribution of blood flow in the rat. Science 126: 1176, 1957.

115. Samuelsson, B. Biosynthesis of prostaglandins. Prog. Biochem. Phamrmacol 5: 109-128, 1969.

116. Sanders, K. M. Endogenous prostaglandin E and contractile activity of isolated ileal smooth muscle. Am. J. Physiol. 234: E208-E212, 1978.

117. Sanders, K. M. Evidence that prostaglandins are local regulatory agents in canine ileal circular muscle. Am. J. Physiol. 246: G361-G371, 1984.

118. Sanders, K. M. and T. E. Northrup. Prostaglandin synthesis by microsomes of circular and longitudinal gastrointestinal muscle. Am. J. Physiol. 244: G442-G448, 1983.

119. Sanders, K. M. and G. Ross. Effects of endogenous prostaglandin E on intestinal motility. Am. J. Physiol. 234: E204-E208, 1978.

120. Sanger, G. J. and A. J. Watt. The effect of PGE^2 on peristalsis and on pervivascular nerve inhibition of peristaltic activity in guinea pig isolated ileum. J. Pharm. Pharmacol. 30: 762-765, 1978.

121. Shehadeh, Z., W. E. Price and E. D. Jacobson. Effects of vasoactive agents on intestinal blood flow and motility in the dog. Am. J. Physiol. 216: 386-392, 1969.

122. Shepherd, A. P. Intestinal capillary blood flow during metabolic hyperemia. Am. J. Physiol. 237: E548-E554, 1979.

123. Shepherd, A. P. Metabolic control of intestinal oxygenation and blood flow. Fed. Proc. 41: 2084-2089, 1982.

124. Shepherd, A. P. and C. G. Burgar. A solid-state arteriovenous oxygen difference analyzer for flowing whole blood. Am. J. Physiol. 232: H437-H440, 1977.

125. Siragar, H. and C. C. Chou. Relative contributions of fat, protein, carbohydrate, and ethanol to intestinal hyperemia. Am. J. Physiol. 242: G27-G31, 1982.

126. Subramanian, N., W. L. Whitmore, F. J. Seidler and T. A. Slotkin. Histamine stimulates brain phospholipid turnover through a direct H-1 receptor-mediated mechanism. Life Sciences 27: 1315-1319, 1980.

127. Sun, F. and B. Taylor. Metabolism of prostacyclin in rat. Biochem. 17: 4096-4101, 1978.

128. Tibblin, S., G. Burns, P. B. Hahnloser and W. G. Schenk, Jr. The influence of vagotomy on the superior mesenteric artery blood flow. Surg., Gyn. and Obstet. 129: 1231-1234, 1969.

129. VanDorp, D. A., R. K. Beerthuis, D. H. Nutgeren and H. Vonkeman. The biosynthesis of prostaglandins. Biochem Biophys Acta 90: 204, 1964.

130. Vane, J. R. and S. Moncada. Polyunsaturated fatty acids as precursors of prostaglandins. Acta Cardiol. (Brux) 23: 21-37, 1979.

131. Vatner, S. F., D. L. Franklin and R. L. Van Critters. Coronary and visceral vasoactivity assocatied with eating and digestion in the conscious dog. Am. J. Physiol. 219: 1380-1385, 1970.

132. Vatner, S. F., D. L. Franklin and R. L. Van Critters. Mesenteric vasoactivity associated with eating and digestion in the conscious dog. Am. J. Physiol. 219: 170-174, 1970.

133. Vatner, S. F., T. A. Patrick, C. B. Higgins and D. Franklin. Regional circulatory adjustments to eating and digestion in conscious unrestrained primates. J. Appl. Physiol. 36: 524-529, 1974.

134. Vogt, W., T. Suzuki and S. Bubilli. Prostaglandins in SR S-C and in darmstoff preparation from frog intestinal dialyates. Mem. Soc. Endocrinol. 14: 137-141, 1966.

135. Von Euler, U.S. Arch Exp Pathol Pharmacol 175:78, 1934.

136. Wallach, D. P. and E. G. Daniels. Properties of a novel preparation of prostaglandin synthetase from sheep seminal vesicles. Biochim Biophys. Acta. 231: 445-457, 1971.

137. Wong, P., J. McGiff, F. Sun and K. Malik. Pulmonary metabolism of prostacyclin in the rabbit. Biochem. Biophys. Res. Comm. 83: 731-738, 1978.

138. Wong, P., F. Sun, K. Malik, L. Cagen and J. McGiff. Metabolism of prostacyclin in the isolated kidney and lung of the rabbit, in Prostacyclin (Eds. Vane and Bergstrom) Raven Press, N.Y., 1979.

139. Wynalda, M.A., W. F. Jigett, and F.A. Fitzpatrick. Sodium 5-(3'-Pyridinylmethyl) Beonzofuran - 2 - Carboxylate (U-63557A), a new, selective thromboxane synthase inhibitor: Intravenous and oral pharmacokinetics in dogs and correlations with ex situ thromboxane B_2 production. Porstaglandins 26: 311-324, 1983.

140 Yagasaki, O., M. Takai, and I. Yanagiya. Release of prostaglandins from the passively distended wall of the guinea pig small intestine. Japan. J. Pharmacol. 30: 853-860, 1980.

141. Yu, Y., C. Luke and C. C. Chou. Distribution of blood flow in the intestine with hypertonic glucose in the lumen. Surgery 78: 520-525, 1975.

142. Zseli, J., T. Topok, S. Vizi and J. Knoll. Effect of prostaglandin E_1 and indomethacin on responses of longitudinal muscle of guinea pig ileum to cholecystokinin. Eur. J. Pharm. 56: 139-144, 1979.