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The Ohio State University, Ph.D., 1974
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SPLANCHNIC HEMODYNAMICS AS RELATED TO
POSTPRANDIAL HUMORAL INFLUENCES

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Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Judith Ann Post, B.Sc.

The Ohio State University
1974

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INTRODUCTION

THE CANINE SPLENCHNIC VASCULAR ANATOMY

In order to understand the physiology of the splanchnic vasculature it is important to have a basic knowledge of its anatomy. Therefore a rather detailed discussion of the arterial and venous vessels of the spleen, small intestine and liver will be presented.

A. Splanchnic Arterial System

The celiac trunk arises as the first visceral branch from the ventral surface of the abdominal aorta (see Figure 1). The celiac's terminal branches are the common hepatic, splenic and left gastric arteries. The common hepatic artery runs craniocaudally and to the right in a groove of the pancreas. The common hepatic sends three to five rather long proper hepatic arteries into the hilus of the liver. These furnish the nutritional blood to the liver (see Figure 2). When three branches are present, the first branch, the right branch goes to the right portion of the liver, the caudate and right lateral lobes. The middle branch goes to the right medial lobe, dorsal part of the quadrate and part of the left medial lobe; this vessel may be replaced by two or more arteries. The left branch, shortest of the three, supplies the large left lateral lobe, the quadrate lobe and part of...
Figure 1. Ventral view of visceral branches of the aorta with their primary anastomoses (86).
Figure 2. Distribution of the proper hepatic arteries (86).
the left medial lobe. The **cystic artery** arises and ramifies into two or more arteries which extend over the surface of the gall bladder, attached to the liver (86).

The **splenic artery** is the branch of the **celiac** which runs to the left and lies in a groove of the left limb of the pancreas near its free end (see Figure 3). The main part of the **splenic artery** approaches the hilus of the spleen near its middle where it sends many branched splenic twigs into the distal half of the gland. The main trunk, now called the **left gastroepiploic artery**, continues in the gastroepiploic ligament to the greater curvature of the stomach (86).

The **cranial mesenteric** or **superior mesenteric artery** is the largest visceral branch of the aorta (see Figures 1 and 4). This unpaired artery arises from the ventral surface of the abdominal aorta about 5 mm caudal to the origin of the **celiac artery**. It is surrounded by the cranial mesenteric plexus of autonomic nerves. The first two branches of the **superior mesenteric artery** arise from opposite sides of the artery about 2 cm from its origin. One of these, the **common colic**, runs cranially in the transverse mesocolon, while the other, the **caudal pancreaticoduodenal** runs to the right and cranially. The remaining part of the **superior mesenteric artery** gradually diminishes in size as some 14 **jejunal arteries** arise from its caudal side. Two **ileal arteries** terminate the **superior mesenteric artery** (86).

As the intestinal arteries radiate into the mesentery, each artery divides into two branches. These branches anastomose with adjacent branches to form arcades. From these primary arcades secondary,
Figure 3. Ventral view of the splenic blood supply (86).
Figure 4. Ventral view of cranial mesenteric artery branches (86).
tertiary, quaternary and more arcades are formed so that a segment of intestine is perfused not by a single source of blood, but by a pool of blood that comes from many branches of an intestinal artery (see Figure 5). Such a vascular pool is seen in the submucosa of the stomach where profuse anastomosis between arteries form an extensive vascular network from which arise the mucosal arteries. In the stomach as in the small intestine, the direction of blood flow in this vascular network can be diverted toward other parts of the mucosa or into other compartments of the gut wall (121). Submucosal arterio-venous anastomoses could play an important role in diverting blood to or away from the intestinal mucosa; however, it has been found by Delaney (1969) that there are very few arterio-venous anastomoses in the mesenteric viscera of the normal dog. Therefore with less than 5 per cent of the total splanchnic blood flow passing through arterio-venous precapillary shunts, it is improbable that they do play an important role in local control of blood flow in these organs (27).

B. Splanchnic Venous System

The splanchnic viscera are drained by the portal vein which with its tributaries forms a true portal system: it arises from a capillary bed and ends in a capillary bed (the hepatic sinusoids) (see Figure 6). It collects blood from the pancreas, spleen and all of the alimentary tract except the esophagus and distal rectum. The portal vein is formed by the confluence of the superior and inferior mesenteric veins and the gastroplenic vein. The superior (or cranial)
Figure 5. Arrangements of the vascular blood supply to the stomach wall. M, mucosal arteries; A, arterial anastomoses; AVA, arteriovenous anastomosis; P, main supply channel of submucous plexus; D, network of anastomoses from which mucosal capillaries arise; S, anastomoses between arteries that pierce muscle (121).
Figure 6. Ventral view of the portal vein (86).
mesenteric vein collects blood from approximately 12 jejunal and ileal veins which accompany their corresponding arteries. The gastrosplenic vein is formed by the confluence of the smaller caudally running left gastric vein and the larger splenic vein (86).

The splenic vein arises by two branches which receive tributaries from the long hilus of the spleen (see Figure 3). The gastro-duodenal vein empties into the portal vein about 1.5 cm from the hilus of the liver. Its chief formative tributary is the cranial pancreatico-duodenal vein. The portal vein divides upon entering the liver, into a small right branch, which is dispersed in the right lateral and right medial lobe, and large left branch, which breaks up in the remainder of the liver (86).

C. The Liver-Structure, Microvasculature and Biliary System

The average weight of the liver, the largest gland of the body, is 3.38 per cent of the body weight of the dog. The hepatic vessels, nerves and bile duct communicate with the liver through the porta or hilus of the liver: the nerves and arteries enter dorsally, the biliary duct leaves ventrally, and the portal vein enters between the two (see Figure 8) (86).

The liver is divided into four lobes and four sublobes as well as two processes, by deeply running fissures (see Figures 7 and 8). The left hepatic lobe forms from one-third to nearly one-half of the total liver mass. It is divided into two sublobes: the left lateral hepatic lobe and left medial hepatic lobe. The quadrate lobe
Figure 7. View of liver, diaphragmatic aspect (86).
Quadratus lobe, Gallbladder
Left lateral lobe
Hepatic v.
L. triangular liga
Difference between liver and gallbladder
Postcava
Caudate lobe
R. triangular liga
Lesser omentum
Coronary liga
Bare area of liver
Caudate process of caudate lobe
Figure 8. View of liver, visceral aspect (86).
is a deep wedge of liver tissue which lies essentially in the median plane. The right hepatic lobe is smaller than the left hepatic lobe and lies completely to the right of the median plane. It is divided into the right medial hepatic lobe and the right lateral hepatic lobe. The caudate lobe is composed of the caudate and papillary processes and the isthmus of liver tissue which connects them (86).

The liver is supplied by both afferent and efferent nerve fibers through the vagi and by sympathetic fibers from the celiac plexus. The hepatic artery receives only sympathetic fibers. Vagal fibers supply the liver parenchyma and biliary system. In some specimens the biliary system receives afferent fibers from the phrenic nerves (86).

The liver substance proper is a tunneled continuum made of liver plates one cell thick and called the muralium simplex (see Figure 9). Lacunae are the tunnels in the muralium which form the hepatic labyrinth. Sinusoids are the specialized capillaries of the liver which form a three dimensional network. Each sinusoid is suspended in a lacuna. The lacuna is not identical with the sinusoid, which occupies its central portion. The peripheral portion of the lacuna is occupied by the perisinusoidal space (pericapillary space) which contains a reinforcing network of reticular fibers. The bile canaliculi form an integral part of the muralium (see Figure 10). They form a continuous net of polygonal meshes which embrace the liver cells and give strength to the muralium (33).
Figure 9. Structure of the liver (33).
Figure 10. Bile canaliculi surrounding liver cells (33).
The blood supply of the liver is derived from two vascular sources: the hepatic artery and the portal vein which both send out branches that empty into the sinusoids. The common portal vein bifurcates into two trunks in the porta hepatis; large branches, the rami venae portae arise from these trunks (see Figure 9). The large branches penetrate into the liver substance and are surrounded by a coat of connective tissue, the continuation of the external capsule. This coat of connecting tissue also carries hepatic arterial branches, bile ducts, lymph vessels and is surrounded by the limiting plate. This roughly cylindrical space containing all of the conduits is called a portal canal. As the rami venae portae branch and rebranch all the other structures contained in the portal canal branch with them (33).

In order to reach the sinusoids, portal blood must pass through the limiting plate (see Figures 9 and 11). Short side branches called inlet venules arise perpendicularly from the portal veins. An inlet sphincter guards each inlet venule. At their extreme ends the smallest portal vein branches lead directly into sinusoids. The most common pattern of sinusoidal arrangement is of the candelabra-type in which can be distinguished peripheral and radial sinusoids. Where a sinusoid empties into a hepatic vein there is an outlet sphincter made up of bulging littoral cells. The smallest hepatic vein rootlet is called a central vein, and all sinusoids empty into central veins. Central veins enter almost perpendicularly into sublobular veins. These converge to form collecting veins which ultimately unite to form the venae hepaticae. The hepatic veins in the dog are surrounded by smooth
Figure 11. Diagramatic representation of the liver vasculature (33).
Constriction of entrance of central into sublobular vein (Popper 1931)

Outlet sphincter (Knisely 1948)

Bulging Kupffer cell (Rüttner and Vogel 1957)

Arteriolar sphincter (Elias 1949)

Inlet sphincter (Knisely 1948)

Sublobular vein

Central vein

Sinusoid

Portal vein

Hepatic artery

Arterial sphincter (Märck 1951)
muscle fibers which constrict when stimulated by various vasoactive sub-
stances (33).

The hepatic arteries branch and accompany the portal vein
branches that run in the portal canals (see Figures 9 and 11). At the
points of branching, the mother vessel is provided with a sphincter.
Minute branches of the hepatic arteries supply the structures lodged in
the portal canals. A second system of arterial branches supplies the
hepatic parenchyma with arterial blood. Long, straight arterial
capillaries arise from the hepatic arteries in the portal canals. These
arterial capillaries send minute branches through the limiting plate to
open into the sinusoids. These arterial capillaries are provided with
sphincters shortly before they enter into the sinusoids (33).

As stated before, the bile canaliculi form a polygonal net
meshwork around the hepatic cells. The hepatic cells of the muralium
produce bile which is discharged into the bile canaliculi. The canali-
culi unite to form the plexiform interlobular ducts which lie in the
interstitial tissue between the lobules (see Figure 9). The interlobu-
lar ducts unite to form the lobar or bile ducts (33). The interlobular
ducts and bile ducts run in the portal canals beside the portal venous
and hepatic arterial branches. The extrahepatic bile passages consist
of the hepatic ducts from the liver, the cystic duct to the gall bladder
and the common bile duct to the duodenum (see Figure 12) (86).

In the study to be presented herein, two surgical preparations
of the canine splanchnic area were used: an isolated denervated in-situ
liver and an isolated segment of the ileum perfused by the terminal por-
Figure 12. Visceral view of the gall bladder and hepatic ducts (86).
Hepatic ducts
Common bile duct
Cystic duct
Caudate process of caudate lobe
Right lat. lobe
Right med. lobe
Quadrate lobe
Left med. lobe
Left lat. lobe
G.
Quadrate lobe

Caudate process

Hepatic ducts

Common bile duct

Cystic duct

Right med. lobe

Left med. lobe

Left lat. lobe

Right lat. lobe

Papillary process of caudate lobe
tions of the denervated superior mesenteric artery and vein. These preparations are used to determine changes in blood flow and vascular resistance that result from the administration of hormonal and chemical agents that are known to be released into the splanchnic circulation after the ingestion of a meal.

CONTROL AND RELEASE OF GASTROINTESTINAL HORMONES AND BILE SALTS

The major portion of this research project deals with the response of the splanchnic vascular bed to several hormonal and chemical substances including pentagastrin, secretin, pancreozymin, sodium taurocholate, sodium dehydrocholate, prostaglandin \( A_1 \) and prostaglandin \( B_1 \). Gastrointestinal hormones and bile salts are released into the splanchnic circulation after the ingestion of a meal. The mechanisms for their release and the control they exert over gastrointestinal secretions and motility will be reviewed. Then their possible role in controlling splanchnic blood flow postprandially will be considered.

There are three phases of gastrointestinal secretion: the cephalic phase mediated by the vagus before the actual ingestion of food; the gastric phase mediated by nervous and hormonal controls by actual presence of food in the stomach; and the intestinal phase mediated by nervous and hormonal controls due to presence of chyme in the duodenum (24).
During the cephalic phase impulses from the vagus (taste and olfactory receptors stimulate the vagus) excite the postganglionic fibers of the myenteric plexus in the stomach. These fibers release acetylcholine which stimulates the mucous, oxyntic and chief cells of the gastric mucosa to secrete mucous, HCl and pepsinogen. The vagal fibers releasing acetylcholine also cause the release of gastrin from the pyloric mucosa which in turn also stimulates the release of HCl and pepsinogen from the gastric mucosa. Acetylcholine and gastrin act synergistically upon the secretory cells of the stomach, so that the magnitude of their response to both agents is far greater than to either alone. Gastrin, circulating through the blood, also stimulates gastric motility, the secretion of bicarbonate-containing fluid from the liver and pancreas, the secretion of enzymes from the pancreas, the release of secretin from the duodenal mucosa and the release of insulin by the beta cells of the pancreatic islets (24).

The actual presence of food in the stomach initiates the gastric phase of gastrointestinal secretion. The gastric phase is mediated through local cholinergic reflex arcs, long reflex arcs of the vagus and by the release of gastrin from the pyloric mucosa. Actual distention of the stomach by food and the presence of protein breakdown products as well as meat extracts from soups, dilute alcohol and caffeine all stimulate gastric secretion of HCl, pepsinogen and gastrin. Carbohydrates and fats do not stimulate gastric secretion other than by distention of the stomach. Gastrin release during the gastric phase of secretion continues the effects on gastric motility, gastric, hepatic
and pancreatic secretions and secretin release that were seen in the cephalic phase. Acid in the pyloric mucosa of the stomach inhibits the release of gastrin; since gastrin stimulates the release of acid, there is present in the stomach itself a negative feedback control for the release of gastrin (24).

In the intestinal phase of gastrointestinal secretion, acid chyme from the stomach enters the duodenum and causes the duodenal mucosa to release the hormone, secretin, which in turn stimulates pancreatic and hepatic secretion of bicarbonate-containing fluid, secretion from the duodenal glands, the release of insulin from the pancreas and the secretion of pepsinogen from the gastric mucosa. Secretin inhibits gastric motility and gastrin-stimulated acid secretion. The presence of protein breakdown products and fat in the chyme that enters the duodenum stimulates the release of the gastrointestinal hormone, cholecystokinin-pancreozymin. Its main actions are the stimulation of secretion of enzymes from the pancreas, contraction of the gall bladder, release of insulin and glucagon from the pancreatic islet cells and the inhibition of gastrin-stimulated acid secretion. Gastrin has a small effect on stimulating pancreatic secretion of enzymes and causing gall bladder contraction, but cholecystokinin-pancreozymin plays the major part in stimulating pancreatic enzyme secretion and gall bladder contraction (24). The effects of the three major gastrointestinal hormones, gastrin, cholecystokinin-pancreozymin and secretin on motility and secretion are summarized in Table 1.
Table 1. Gastrointestinal hormones and their effects on gastrointestinal secretion and motility (24).
### Gastrointestinal Hormones

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Gastrin</th>
<th>Cholecystokinin-Pancreozymin</th>
<th>Secretin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>pyloric mucosa</td>
<td>duodenal mucosa</td>
<td>duodenal mucosa</td>
</tr>
<tr>
<td>Release Stimulated By</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Vagal stimulation - ach.</td>
<td>1. protein breakdown products</td>
<td>1. gastrin</td>
<td></td>
</tr>
<tr>
<td>2. Distention of stomach</td>
<td>in duodenum</td>
<td>2. acid in duodenum</td>
<td></td>
</tr>
<tr>
<td>3. Presence in stomach of:</td>
<td>2. fats in duodenum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Protein</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b. Alcohol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c. Meat extract</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>d. Caffeine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Release Inhibited By</td>
<td>acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>1. Acid secretion</td>
<td>1. acid secretion</td>
<td>1. --------</td>
</tr>
<tr>
<td>2. Pepsinogen secretion</td>
<td>2. pepsinogen secretion</td>
<td>2. Pepsinogen secretion</td>
<td></td>
</tr>
<tr>
<td>3. Lower esophageal sphincter</td>
<td>3. --------</td>
<td>3. --------</td>
<td></td>
</tr>
<tr>
<td>4. Antral motility</td>
<td>4. antral motility</td>
<td>4. --------</td>
<td></td>
</tr>
<tr>
<td>5. HCO₃⁻ secretion</td>
<td>5. HCO₃⁻ secretion</td>
<td>5. HCO₃⁻ secretion</td>
<td></td>
</tr>
<tr>
<td>7. HCO₃⁻ secretion</td>
<td>7. HCO₃⁻ secretion</td>
<td>7. HCO₃⁻ secretion</td>
<td></td>
</tr>
<tr>
<td>Duodenum and small intestine</td>
<td>10. Motility</td>
<td>10. Motility</td>
<td>10. --------</td>
</tr>
<tr>
<td>11. Secretin release</td>
<td>11. --------</td>
<td>11. --------</td>
<td></td>
</tr>
<tr>
<td>Inhibits</td>
<td>Ileocolic sphincter</td>
<td>Gastrin stimulated acid secretion</td>
<td>1. Gastrin stimulated acid secretion</td>
</tr>
<tr>
<td>2. Lower esophageal sphincter</td>
<td>2. Lower esophageal sphincter</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Gastric and intestinal motility</td>
<td>3. Gastric and intestinal motility</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic Effects</td>
<td>1. Releases Insulin</td>
<td>1. Releases Insulin</td>
<td>1. Releases Insulin</td>
</tr>
<tr>
<td>2. Releases glucagon</td>
<td>2. Releases glucagon</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Lipolysis in adipose tissue</td>
<td>3. Lipolysis in adipose tissue</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Key: Strongest effects, strong effects, weak effects*
Structures of secretin, pancreozymin and gastrin pentapeptide, the hormonal substances used in this study, are given in Figure 13. Pancreozymin and pentagastrin contain the same C-terminal sequence, and since the action of the hormones is very likely through a combination of the C-terminal group with a specific receptor site in the effector cells, gastrin and cholecystokinin as predicted have the same spectrum of activities. Because the remainder of the pancreozymin molecule differs from that of gastrin, they have quantitatively different actions (see Table 1). Gastrin and pancreozymin act thus as competitive inhibitors of one another. Secretin, which has none of the structure of gastrin, acts as a non-competitive inhibitor of gastrin because it has some of the same actions as gastrin but combines with a different receptor site. Secretin has a structure similar to glucagon. Both mediate the same effects on gastrointestinal secretion and motility but the effects differ quantitatively. Glucagon generally induces quantitatively weaker effects than does secretin (24).

Bile secretion is under chemical, humoral and nervous control. Bile is continuously secreted into the bile canaliculi and from there flows into the hepatic ducts and is stored and concentrated in the gall bladder between meals. The two major components of bile, the bile salts and bicarbonate fluid are under separate controls. The rate of flow of the bile from the liver is governed by the actual rate of secretion of the bile salts themselves. The second component, an isotonic fluid containing sodium, chloride and bicarbonate, has its rate of flow in part controlled by secretin, and possibly other hormones. Bile salts
Figure 13. Structures of the gastrointestinal hormones pancreozymin and secretin and synthetic gastrin pentapeptide (24).
STRUCTURES OF HORMONES

GASTRIN PENTAPEPTIDE

\[
C(CH_3)_3 \text{- CO-NH-CH}_2 \text{- CH}_2 \text{- CO-Trp-Met-Asp-Phe-NH}_2
\]

CHOLECYSTOKININ - PANCREOZYMIN

\[
(25 \text{ more}) \text{- Asp-Tyr-Met-Gly-Trp-Met-Asp-Phe-NH}_2
\]

SECRETIN

\[
\text{His-Ser-Asp-Gly-Thr-Ser-Thr-Ser-Glu-Leu-Ser-Arg-Leu-Arg-}
\text{- Asp-Ser-Ala-Arg-Leu-Gin-Arg-Leu-Leu-Gin-Gly-Leu-Val-NH}_2
\]
themselves are powerful choleretics. When infused intravenously they are removed from the blood by the parenchymal cells of the liver to cause increased active output of bile salts and passive flow of water and electrolytes into the bile, such that the bile salt concentration may increase as well as the volume output. When the rate of infusion of bile salts is increased, the rate of flow of bile also increases. Taurocholate, a natural, conjugated primary bile acid, has been shown to be an effective choleretic (96, 115). Sodium dehydrocholate, an oxidized, non-conjugated bile salt has been found to be a very effective hydrocholeretic (47, 98), producing a copious flow of thin watery bile.

Secretin is known to be a hydrocholeretic in the dog (53, 65, 96, 115). It stimulates the increased flow of bicarbonate-containing fluid without increasing the bile salt concentration. Of the many studies done on the choleretic effects of gastrin none are in total agreement. Gastrin has been shown to be a choleretic in the dog only if the enterohepatic circulation of bile acids is maintained by infusing taurocholate (66, 106). Some believe that gastrin is not an important physiologic choleretic (76, 103) whereas others give gastrin a more important role as a choleretic (88, 136). Gastrin, acting by two routes, stimulates bile flow by direct action on the liver and by indirect action on the duodenum to release secretin (24). Pancreozymin has been shown to be a stronger choleretic than gastrin II (66), but is only one-half as potent as secretin (24).

Stimulation of the vagus also increases bile secretion by the direct action of acetylcholine. Since vagal stimulation releases
gastrin, some of the effects of the vagal reflexes on bile flow must be mediated by that hormone.

Contraction of the gall bladder, which stores and concentrates the bile between meals, is under nervous and humoral control. During the cephalic phase of digestion, vagal stimulation reflexly causes the gall bladder to contract, raising the pressure of bile within the ducts. The sphincter of Oddi opens and bile empties into the duodenum. Cholecystokinin also acts as a cholecystogogue, a substance prompting the discharge of gall bladder bile. Gastrin is a relatively weak cholecystogogue compared to cholecystokinin. Within 30 minutes after ingestion of a meal, chyme in the duodenum causes the release of cholecystokinin which together with gastrin and vagal reflexes causes the gall bladder to empty its bile into the duodenum. The bile salts, which are powerful detergents, assist in the emulsification, hydrolysis and absorption of fats. Most of the bile salts are then reabsorbed in the ileum, pass into the portal blood and are carried to the liver cells which then actively secrete again into the bile canaliculi (24).

The primary bile acids in mammalian species are cheno-deoxycholic acid and cholic acid - non-conjugated bile acids which are biosynthesized in the liver from cholesterol. They can be conjugated with either glycine or taurine and can be changed from bile acids to bile salts by the addition of a cation such as sodium. In the present study a conjugated bile salt, sodium taurocholate, which is a combination of cholic acid and taurine, and a non-conjugated oxidized bile salt, sodium dehydrocholate which is a synthetic derivative of cholic acid
(see Figure 14) (514, 109, 119) were tested for their choleretic and hemodynamic effects.

EFFECTS OF NATURALLY OCCURRING VASOACTIVE AGENTS ON THE HEMODYNAMICS OF THE LIVER AND SMALL INTESTINE

Before discussing the work that has been done on splanchnic hemodynamics involving the gastrointestinal hormones, bile salts and prostaglandins, the results of research involving the effects of several other naturally occurring vasoactive agents on regional splanchnic hemodynamics will be discussed.

Blood flow, \( Q \), is determined by several factors. It is directly proportional to the pressure head \( (P_1 - P_2) \) of the blood vessel, to the fourth power of the radius \( r \) of the vessel and is inversely proportional to the vessel length \( L \) and the viscosity of the blood \( \eta \) as expressed in Poiseuille's law:

\[
Q = \frac{(P_1 - P_2) \pi r^4}{\eta 8L}.
\]

Vascular resistance \( R \) is defined as the ratio of the pressure head \( (P_1 - P_2) \) to the flow \( Q \). Thus from Poiseuille's law:

\[
R = \frac{\eta 8L}{\pi r^4}.
\]

Since the pressure head is generally kept constant, the flow to a circulation is determined primarily by the vascular resistance,
Figure 14. Structures of the bile acids cholate, taurocholate and dehydrocholate (54, 109, 119).
BILE ACID STRUCTURES

CHOLIC ACID

TAUROCHOLATE

DEHYDROCHOLATE
which is directly proportional to the vessel length and blood viscosity and inversely proportional to the fourth power of the radius of the vessel (121).

The vessel radius, which can be altered either actively or passively, is normally the main determinant of vascular resistance. A passive change in vessel radius can be produced by altering the transmural pressure of a vessel. The transmural pressure is the difference between the intraluminal pressure and the extraluminal pressure. An increase in transmural pressure may be caused by either raising the intraluminal pressure or lowering the extraluminal pressure. This results in an increase in vessel radius, a decrease in vascular resistance and an increase in blood flow providing the pressure head remains constant. A fall in transmural pressure will produce the opposite results (121).

Vascular extraluminal pressure may play an important role in the regulation of blood flow in the splanchnic circulation. Changes in gastrointestinal motility can passively alter the radii of the intramural vessels. When intestinal smooth muscle contracts, vascular extraluminal pressure is increased resulting in a fall in vascular transmural pressure (if intraluminal pressure is not raised proportionally) and a decrease in vessel radius (121).

Active changes in vessel radius in response to neural, chemical or physical stimulation are the most important determinants of vascular resistance (121). The net change in vessel radius during the intraarterial infusion of a vasoactive agent, for example, depends upon three
local effects (8): an active change in vessel radius due to a direct effect on the vascular smooth muscle (121), an active change in vessel radius due to the accumulation of vasoactive metabolites produced, stored and utilized by the parenchymal cells (46) and a passive change in vessel radius due to a change in vascular transmural pressure due to a change in the mechanical activity of the intestinal smooth muscle (48). The effects of several vasoactive substances upon resistance in the small vessel segment of the canine small intestinal vascular bed during their infusion into the superior mesenteric artery is summarized in Figure 15.

Acetylcholine

Acetylcholine or synthetic cholinergic drugs such as mecholyl actively contract intestinal smooth muscle but relax intestinal vascular smooth muscle. In the dog they actively dilate the intestinal vessels (8, 122). The intra-arterial injection of 1 μg of acetylcholine into the superior mesenteric artery of the dog results in a decrease in intestinal vascular resistance while a larger 10 μg dose results in an increase in intestinal vascular resistance (121). The 1 μg dose actively vasodilates the intestinal vessels without increasing intestinal motility. The 10 μg dose causes an increase in intestinal motility, which has the mechanical effect of decreasing the transmural pressure of the vessels to produce an increase in vascular resistance (8, 122).

In general, acetylcholine in adequate doses causes vasodilation of the hepatic arterial bed, providing it is not already maximally
dilated. Portal venous resistance increases or is not significantly changed by acetylcholine infusion (46). In the dog local infusion of acetylcholine decreases hepatic arterial resistance, does not affect portal venous resistance, but increases hepatic venous resistance somewhat (121).

Catecholamines

Generally the net effect of epinephrine is to directly constrict intestinal vascular smooth muscle and relax visceral smooth muscle (48, 122). Epinephrine and levarterenol (1-norepinephrine) when infused into the superior mesenteric artery of the dog cause both large and small arterial vasoconstriction in the small intestine (122). When visceral smooth muscle is active, intra-arterial injection of epinephrine causes a decrease in intestinal vascular resistance; when visceral smooth muscle is relatively inactive, intra-arterial injection of epinephrine results in an increase in intestinal vascular resistance (48). Since epinephrine actively constricts intestinal vascular smooth muscle, when its administration apparently results in a decreased vascular resistance, the effect is, very likely in part due to active relaxation of the visceral smooth muscle, which passively causes the vessel radius to increase by decreasing vessel extraluminal pressure. Epinephrine also increases the metabolism of the parenchymal cells producing vasodilator metabolites which may play a role in causing the vasodilation seen. When the net effect of epinephrine on the gut is an apparent increase in vascular resistance, it is the result of its direct
vasoconstrictor activity, since the visceral smooth muscle is at the same time relaxed which should tend to passively increase vessel transmural pressure (121).

It has been shown that there are alpha-adrenergic receptors in the small intestine of the dog which respond to catecholamines with a resulting active vasoconstriction. Blockade of the alpha-adrenergic receptors with an alpha-adrenergic blocking agent such as azapetine umasks the presence of beta-adrenergic receptors, which when acting alone respond to catecholamines by eliciting a resulting vasodilation. These responses have been demonstrated in the small intestinal vasculature of the dog (48). At low concentrations, epinephrine stimulates only the beta receptors to produce intestinal vasodilation. At higher concentrations epinephrine stimulates both alpha and beta receptors; however, the alpha receptor effect is usually dominant over that of the beta receptors and the net effect is active vasoconstriction (121). When vasodilation of the intestinal vasculature occurs during catecholamine stimulation, the vasodilation is caused in part by beta-adrenergic receptor stimulation, by indirect mechanical effects of relaxed visceral smooth muscle, and by metabolic vasodilators released from the parenchymal cells.

It has been established that there are alpha and beta adrenergic receptors in the hepatic arterial vasculature, also. Local infusions of catecholamines into the canine hepatic artery generally result in an increased resistance in this vascular bed. This vasoconstriction can be prevented by infusing phentolamine, an alpha-adrenergic blocking
agent (30, 46, 121). There are also alpha-adrenergic vasoconstrictor receptors in the portal vein, but these react to catecholamines with a weaker vasoconstriction (51, 121). Beta-adrenergic vasodilator receptors are present in the canine hepatic arterial bed as demonstrated by the vasodilation that occurs when isoproterenol, a beta-adrenergic stimulator, is infused into the hepatic artery (30). By administering propranolol, a beta-adrenergic receptor blocking agent, the vasodilation achieved in the hepatic artery with isoproterenol administration can be abolished. However, there seems to be little evidence for the presence of beta-adrenergic receptors in the canine portal vein, since the infusion of isoproterenol produces little effect on intrahepatic portal venous resistance (51). Epinephrine dilates the hepatic venous vascular bed resulting in great hepatic venous outflow and a decreased liver weight in the dog (121). The predominant splanchnic vascular effect of low intravenous doses of epinephrine is a marked increase in portal venous and total hepatic flow due to stimulating of beta-adrenergic vasodilator receptors in the small intestine (46).

Histamine

The mucosa of the gastrointestinal tract contains a high concentration of histamine, an autacoid that stimulates gastric secretion, dilates blood vessels and is involved in local edema formation and anaphylactic shock (121). Infused intra-arterially, histamine dilates the arteries of the intestine in the dog and cat (100, 122). If infused intravenously, however, it stimulates the release of catecholamines
from the adrenal medulla which then constrict the intestinal vascular bed (100, 121).

Histamine infused into either the hepatic artery or portal vein of the dog or cat produces marked vasodilation of the hepatic arterial bed. In dogs, histamine constricts the hepatic venous bed to cause outflow block in the liver (46, 121).

Serotonin

About 90 per cent of the serotonin present in the human body is stored in the gastrointestinal mucosa (121). Serotonin infused into the superior mesenteric artery of the cat or dog, constricts the large mesenteric arteries and dilates the smallest ones (6, 121, 122). Serotonin contracts visceral smooth muscle and similar to acetylcholine it can produce an increase, no change or a decrease in gastrointestinal blood flow, depending upon the interplay between its vasodilator effect on vascular smooth muscle and its stimulatory effect on visceral smooth muscle (121). A precursor of serotonin, 5-hydroxytryptamine, may be involved in mediating the increase in splanchnic blood flow that occurs after the administration of pancreozymin or secretin in the cat (6). Little is known about the effects of serotonin on the hepatic vascular bed. In the dog infusion of serotonin caused a small decrease in total hepatic flow, and in isolated perfused canine livers both hepatic arterial and portal venous resistances were increased after serotonin administration. However, serotonin does not constrict the hepatic veins to cause hepatic outflow block (46).
Angiotensin

Angiotensin II, an octapeptide, as a vasoconstrictor, is more potent than the catecholamines (122). The enzyme renin, released from the kidney, acts on angiotensinogen, a plasma alpha-2 globulin, to form inactive angiotensin I, the precursor of angiotensin II. Angiotensin II, infused into the superior mesenteric artery of the dog, constricts the small artery segment of the small intestine (121, 122).

In both the bovine and canine liver, local infusions of angiotensin constrict both the hepatic arterial and portal venous vascular beds with a decrease in liver weight. The fall in portal flow is also due to small intestinal and splenic vasoconstriction (46, 73, 121).

Plasma Kinins

Bradykinin is a nonapeptide and kallidin a decapeptide. Both are potent vasodilators and are formed when proteolytic enzymes, kallikreins, act on kallidinogen, a plasma alpha-2-globulin. Plasma kinins have been postulated to play roles in salivary and pancreatic secretion, in shock, in edema formation and in the ischemic bowel syndrome. Bradykinin has the most potent vasodilator effect on the intestine of all naturally occurring endogenous agents. When infused intra-arterially it produces vasodilatation in the stomach and small intestine (121). Local infusions of bradykinin increase hepatic arterial flow in the dog and cause a small decrease in liver weight (46, 121).
Vasopressin

Vasopressin, a purified preparation of ADH, is the most potent naturally occurring vasoconstrictor with respect to action on the superior mesenteric circulation (121). Infused intra-arterially into the mesenteric bed of the dog, vasopressin constricts the arteriolar vasculature of the small intestine (49, 121, 122). It also constricts the gastric and splenic vasculatures and decreases gastric, biliary and pancreatic secretions possibly because of the decreased blood flow (121). Infused systemically, vasopressin produces an increase in the fraction of the cardiac output which perfuses the brain, eyes, kidneys, heart and hepatic artery at the expense of blood flow to other organs (36).

Local infusions of vasopressin into the liver of the dog result in hepatic arterial vasoconstriction and no significant effect on portal venous vascular resistance or total liver blood volume (46, 121). However, intravenous infusions of vasopressin result in hepatic and mesenteric arterial vasoconstriction which leads to a fall in portal venous pressure and a fall in total liver blood flow in the human (121). Vasopressin infused into the femoral vein of the dog produced an initial decrease in hepatic arterial flow followed by an increase in flow above control values. The secondary vasodilator response is attributed to build-up of vasodilator metabolites in the hepatic vasculature or to the myogenic vasodilator response that occurs in the hepatic artery when blood flow is reduced in the portal vein (46, 49). Portal venous flow is definitely reduced due to intestinal and splenic vasoconstriction produced by the infusion of vasopressin,
which is the only pressor substance known to produce a decrease in portal venous pressure (36).

Cations

Three of the four major cations in the body - potassium, magnesium and calcium - are vasoactive. Depending upon the concentration of potassium infused, it has a biphasic effect on canine renal, forelimb, coronary and mesenteric vascular beds. Infused into the canine superior mesenteric artery, isotonic KCl solution decreases arteriolar vascular resistance in the small intestine. If the blood concentration of infused potassium is above 10 mEq/L, the mesenteric vasculature constricts. K⁺ at all concentrations produces only vasodilation in the gastric vasculature (121, 123). The potassium ion also exerts a biphasic effect on the visceral smooth muscle of the small intestine. Intestinal wall tension is decreased at low blood concentrations of potassium and is increased at higher concentrations. Thus the indirect mechanical effect of potassium on vessel radii in the small intestine is additive to its direct effect at all infusion rates (121).

At low infusion rates potassium dilates the canine hepatic arterial system if preinfusion vascular resistance is high; however, at higher infusion rates, potassium constricts the hepatic arterial system and markedly reduces liver weight (19, 121). Portal venous resistance in the dog is unaffected by local infusions of KCl (19).

Isotonic MgCl₂ infused intra-arterially decreases intestinal and gastric vascular resistances in the dog (121, 123). It also relaxes
visceral smooth muscle which passively dilates blood vessels. This passive vasodilator effect of magnesium augments its active vasodilator effect on the gastrointestinal vasculature (121). Magnesium whether infused directly into the hepatic artery or the portal vein of the canine liver dilates the hepatic arterial bed but does not change liver weight. In the dog it causes no change in portal venous flow or resistance (19, 121).

In the dog intra-arterial infusions of calcium increase intestinal, kidney, heart and forelimb vascular resistance and decrease gastric vascular resistance (121, 123). It reduces intestinal wall tension, and thus, this passive decompression effect on the intestinal vasculature attenuates the active vasoconstrictor effect of calcium in the small intestine (121). In the dog isotonic CaCl₂ infused into the hepatic artery does not change hepatic arterial resistance or liver weight, and when infused into the portal vein, isotonic CaCl₂ does not affect portal venous resistance (19).

Metabolites

High local blood concentrations of carbon dioxide actively dilate jejunal blood vessels while lower than normal concentrations may cause constriction. Carbon dioxide actively contracts visceral smooth muscle to indirectly decrease intestinal blood flow (121). Introducing a gas high in carbon dioxide content into loops of the small intestine increases superior mesenteric artery flow in dogs; the increase is directly proportional to the increase in intraluminal carbon dioxide content (121).
In dogs infusions of ATP, ADP, AMP or adenosine into the superior mesenteric artery produces vasodilation (121). Intravenous infusions of adenosine increase portal flow and pressure due to intestinal vasodilation in the canine. Local infusions of adenosine into either the hepatic artery or portal vein cause an increase in hepatic arterial flow (46).

Intestinal vascular resistance can be affected by the above metabolic vasodilators released from the parenchymal cells. Local concentrations of metabolites can be altered by altering local blood flow rates if metabolism and the release of metabolites remain at the same rate. A fall in local blood flow tends to increase the local concentration of metabolites which acts to cause vasodilation and an increase in blood flow which subsequently removes the vasodilator metabolites from the area again allowing the vessel to decrease its radius (121).

Glucagon

Glucagon is well-established as a vasoactive polypeptide. In dogs, cats and monkeys infusions of glucagon cause an increase in intestinal blood flow and hepatic arterial blood flow (9, 39, 82). In the cat given intra-arterially glucagon also inhibits gastrointestinal motility which may augment the intestinal vasodilator response (39). In dogs, besides increasing hepatic arterial flow, glucagon increases portal venous pressure (82). In rhesus monkeys glucagon causes total liver blood flow to more than double (9).
Injections of hypertonic glucose into the lumen of the proximal jejunum is known to increase jejunal blood flow. In isolated segments of canine jejunum, intraluminal placement of hypertonic glucose solutions caused an increase in blood flow that was a local response confined to the area of gut perfused by the glucose solution (18, 21, 130). In isolated segments of duodenum as well, hypertonic but not isotonic glucose solutions placed intraluminally caused a local increase in intestinal blood flow (20).

See Figure 15 for a summary of the effects of many of the above intra-arterially infused vasoactive chemicals on small vessel resistance of the canine small intestine.

EFFECTS OF EATING AND DIGESTION ON MESENTERIC HEMODYNAMICS

Several studies have been done concerning regional blood flow changes in the dog before and after the ingestion of a meal. Herrick (1934), using a thermoströmuhrl, studied blood flow changes that occurred in the femoral, carotid and mesenteric arteries and the external jugular vein of previously fasted dogs during and following the ingestion and digestion of a meal. Blood flow increased in the femoral artery 10-15 minutes after the ingestion of food, continued at a high level for 1.5 to 2.5 hours and gradually decreased to the fasting level by 6 hours postprandially. Both the carotid artery and external jugular vein
Figure 15. Effects of various agents infused via the superior mesenteric artery on the small vessel resistance (R<sub>SV</sub>) of the canine small intestine (121).
exhibited a great postprandial increase in blood flow. Blood flow in the superior mesenteric artery increased 62 per cent by 90 minutes after the ingestion of food. Herrick postulated that the increase in regional blood flow seen during digestion is due to either the specific dynamic action of food, a product of digestion, a secretagogue or a hormone of the gastrointestinal tract (58).

Burns and Schenk (1967) examined the effect of digestion and exercise on superior mesenteric artery blood flow in the conscious dog by using an electromagnetic blood flowmeter. They found that mesenteric blood flow increased 65 per cent after 1 hour and was maintained at a high level for 3 hours after the ingestion of a meal. There was no postprandial increase in cardiac output despite the increase in mesenteric blood flow. Thus they concluded that the increase in mesenteric blood flow was a regional phenomenon. They tested the effects of gastrin and secretin on mesenteric blood flow and found that both produced an increase in blood flow in that region (17).

Vatner (1970) also studied the effects of eating and digestion on mesenteric blood flow and resistance in the conscious dog as well as measuring cardiac output, heart rate and aortic blood pressure pre- and postprandially. The anticipation of ingestion, or the cephalic phase of eating, was characterized by transient increases in cardiac output (63 per cent), heart rate (78 per cent) and aortic blood pressure (31 per cent) and a transient decrease in mesenteric blood flow. During the digestive phase, cardiac output, arterial blood pressure and heart rate returned to control levels, while mesenteric blood flow began to
increase 5-15 minutes postprandially, peaked after 30-90 minutes at 115 to 300 per cent over the control value and gradually returned to control within 3-7 hours after eating. During the digestive phase in the resting dog, there was a slight vasoconstriction of the skeletal muscle vasculature. Vatner states that the sympathetic nervous system is responsible for the increase in cardiac output, heart rate, aortic blood pressure and mesenteric resistance seen in the cephalic phase but that it is not involved in the mesenteric vasodilation seen during the digestive phase. The latter was prevented by cholinergic blockade but not by alpha or beta adrenergic blockade or bilateral thoracic vagotomy (131, 132).

It has been established that there is a postprandial increase in mesenteric blood flow in the dog; however, the cause of this is as yet not understood. Since the gastrointestinal hormones secretin, gastrin and pancreozymin, as well as bile salts and protein digestion products, enter the mesenteric circulation of the dog postprandially, it is possible that the increase in mesenteric blood flow may be due to one or more of these agents.

THE EFFECTS OF GASTROINTESTINAL HORMONES, BILE SALTS AND PROSTAGLANDINS ON SPLANCHNIC HEMODYNAMICS

Since the present study is concerned with the hemodynamic effects of secretin, pentagastrin, pancreozymin, sodium taurocholate, sodium dehydrocholate and several of the prostaglandins, some of the
pertinent literature will be briefly reviewed. A certain amount of work has been done involving the effects of these agents on pancreatic and small intestinal hemodynamics in the dog and other species, but very little information is available as to effects on hepatic hemodynamics.

Secretin

Several researchers have studied the effects of secretin on pancreatic blood flow and exocrine secretion, and have found that in the cat, dog and human, secretin produces both an increase in pancreatic blood flow and exocrine secretion (2, 40, 42, 44, 57, 95, 128). There is conflicting evidence as to whether or not the rise in pancreatic blood flow after secretin administration is associated with an increase in pancreatic metabolic activity. Pure Jorpes secretin injected at 1 U/kg produced an increase in pancreatic oxygen consumption in the dog (42); however, another study using dogs showed that there was no increase in pancreatic metabolic activity after secretin administration even though there was an increase in pancreatic blood flow and exocrine secretion (40). Since there was no change in systemic arterial blood pressure or cardiac output after secretin injection (40), and it is postulated that the vasodilator effect of secretin on the pancreas is not a direct one, the vasodilation is thought to be due to the release of a local vasoactive agent such as bradykinin (40, 44, 64) or histamine (95).

Secretin has also been found to increase blood flow to the small intestine in the cat and human (6, 37, 38, 64, 102). Secretin in-
jected either intravenously or intra-arterially caused vasodilation in the small intestine of the cat without altering systemic blood pressure or cardiac output (6, 37, 38, 102). One source concludes that secretin is a direct vasodilator when injected into the cat superior mesenteric artery (102), while others conclude that the vascular effect is secondary to the metabolic effect of secretin, the metabolic products released directly causing the increase in blood flow (37, 38). Still another theory is that 5-hydroxytryptamine, the precursor of serotonin is caused to be released, and this directly results in intestinal vasodilation in the cat, since the blood flow increase seen after secretin infusion was abolished when the vasodilator effect of 5-hydroxytryptamine was blocked by dihydroergotamine (6). Secretin does not greatly effect small intestinal motility in the cat (37, 38); therefore, mechanical effects of the visceral smooth muscle on the intestinal blood vessels is not likely a significant factor. It was also found that intestinal vasodilation produced after secretin administration was not changed by alpha receptor, beta receptor or cholinergic receptor blockade in cats (6, 37). No work has been done involving the effects of secretin on intestinal vascular resistance in the dog.

In the human secretin administration does not affect the radius of the hepatic artery, but increases the radius of the portal vein (128). In the cat close intra-arterial injection of secretin has been reported to cause a decrease in hepatic arterial flow (102). This is the extent of the work that has been done with secretin on hepatic hemodynamics.
Pancreozymin

Pancreozymin causes an increase in pancreatic blood flow in the dog (2, 40, 44, 95) but no increase in cardiac output (48). The increase in pancreatic blood flow due to pancreozymin infusion is thought to be an indirect effect due to the release of local vasodilators such as plasma kinins (40, 44) or histamine (95). Pancreozymin is known to increase small intestinal motility (38, 55) and decrease small intestinal vascular resistance in the cat without changing aortic pressure or heart rate (6, 37, 38). In one study the administration of atropine blocked small intestinal motility effects usually induced by pancreozymin infusion, allowing the transient increase in intestinal blood flow to be prolonged, since the mechanical compression effect of the visceral smooth muscle was removed (6). The intestinal vasodilator effect of pancreozymin is postulated to be indirectly due to 5-hydroxytryptamine (6) or the release of other vasodilator metabolites (37), since pancreozymin increases the metabolic activity of the small intestine. Pancreozymin appears to be inactivated in both the pancreas and liver of the dog (95), but there have been no studies on the effects of pancreozymin on the hepatic vasculature.

Pentagastrin

Infusion of pentagastrin in the dog produces an increase in pancreatic blood flow and perfusion rate but no increase in cardiac output (44). Pentagastrin infused into the superior mesenteric artery of
the cat causes a transient increase in intestinal blood flow and an increase in small intestinal motility. Pentagastrin infusion followed by atropine administration results in a sustained increase in intestinal blood flow thereby demonstrating that increased intestinal motility ordinarily will passively attenuate the active vasodilator response (38). Pentagastrin has been found to be inactivated in the liver of the rat (120) and the dog (124) by hepatic amidase, but there have been no studies done to determine the effects of pentagastrin on liver blood flow.

Sodium Dehydrocholate

Sodium dehydrocholate injected into the superior pancreatic-duodenal artery of the dog significantly increases pancreatic blood flow (95). When infused into the femoral vein of the dog, sodium dehydrocholate transiently increases and then decreases flow in the superior mesenteric artery (47). Intravenous administration has also been reported to cause an increase in hepatic arterial flow in the dog (47, 87) and a decrease in portal venous flow so that there is little change in total liver blood flow (47). In human subjects intravenous injections of sodium dehydrocholate result in an increase in total liver blood flow accompanied by no change in portal venous pressure (87). In the dog it also causes a fall in systemic blood pressure (98).
Sodium Taurocholate

One study has been done on the effects of sodium taurocholate infusion on the splanchnic hemodynamics of the dog. Femoral vein infusion of this bile salt produced a decrease in hepatic arterial blood flow. It has been postulated that only hydrocholeretics such as sodium dehydrocholate produce an increase in liver blood flow while true choleretics such as sodium taurocholate do not (47).

Prostaglandins

Chemistry and Structures

Biosynthesis

Prostaglandin was first isolated from the seminal vesicles and plasma by Goldblatt and von Euler in the early 1930's. The chemical structures and the biosynthesis of the prostaglandins were elucidated by Bergstrom from 1957 to 1964. Fourteen naturally occurring prostaglandins have been isolated and grouped on the basis of their structures: E, F, A and B groups. There are 6 members of the E and F groups: \(E_1, E_2, E_3, F_1\alpha, F_2\alpha\) and \(F_3\alpha\) which are considered primary compounds because none of these is derived from any of the others. The remaining 8 prostaglandins are derived from the primary compounds through alterations in structure. The numerical subscripts represent incorporations of 1, 2 or 3 double bonds. See Figure 16 for structure representations (79, 97).

All of the prostaglandins are 20 carbon, hydroxylated fatty acids with a cyclopentane ring and two side chains and are derivatives
Figure 16. Structures of the prostaglandins E, F, A and B \((89, 97)\).
PROSTAGLANDINS — STRUCTURES

prostanoic acid

PGE₁

PGE₂

PGF₁α

PGF₂α

PGA₁

PGA₂

PGB₁

PGB₂
of prostanoic acid. Prostaglandins are biosynthesized from poly-
unsaturated essential fatty acids: di-homo-γ-linoleic acid is the pre-
cursor for PGE\textsubscript{1} and PGF\textsubscript{1α} and arachidonic acid is the precursor for
PGE\textsubscript{2} and PGF\textsubscript{2α}. They stem from a common cyclic endoperoxide inter-
mediate \(79, 84\). Since the most abundant essential fatty acid in the
body is arachidonic acid, the majority of tissues contain mostly PGE\textsubscript{2}
and PGF\textsubscript{2α}. The prostaglandins A and B are derived from the prosta-
glandins E through dehydration. The prostaglandins B may also be de-
derived from the prostaglandins A through isomerization. Unlike biogenic
amines, prostaglandins are not stored in the body, but are formed im-
mediately prior to release. A variety of physiological, pharmacological
and pathological stimuli trigger the activation of phospholipase A,
which splits the precursor essential fatty acids from the phospholipids
in the cell membrane. The underlying mechanism through which phosho-
lipase A is activated by these stimuli remains unknown. Prostaglandin
formation is catalyzed by the microsomal multi-enzyme system loosely
called prostaglandin synthetase \(89\). Coenzymes such as catecholamines
and serotonin and various cofactors and oxygen are required to complete
and regulate the biosynthesis of the prostaglandins. See Figure 17 for
the biosynthesis \(79, 84, 89, 97\).

Breakdown

After exerting their biological actions, newly synthesized
prostaglandins are rapidly metabolized by tissues such as the lungs,
kidneys, liver and intestines. The lung is the major site of prosta-
Figure 17. Biosynthesis of the prostaglandins E, F, A and B (79, 84, 89, 97).
PROSTAGLANDIN BIOSYNTHESIS

PHOSPHOLIPIDS (LECITHIN) → PHOSPHOLIPASE A

POLYUNSATURATED FATTY ACIDS

ARACHIDONIC ACID → DI-HOMO-δ-LINOLEIC ACID

PROSTAGLANDIN SYNTHETASE

O₂, COFACTORS

PGE₂ → PGF₂α → H⁺, OH⁻, DEHYDRATION

PGA₂ → PGB₂

ISOMERIZATION

PGE₁ → PGF₁α → H⁺, OH⁻
glandin inactivation. The lung contains 15 hydroxy-prostaglandin dehydrogenase which oxidizes the prostaglandins and is the most effective enzyme for inactivating the prostaglandins. Fifteen hydroxy prostaglandin dehydrogenase metabolizes the PGE and PGF compounds more efficiently than it does the PGA compounds, since the PGA's emerge from the pulmonary circulation with relatively little loss of activity (89, 105). Proof of this has been shown in the cat and dog. In the dog prostaglandins A\textsubscript{1} and A\textsubscript{2} increased renal blood flow whether injected intravenously or intra-arterially whereas the prostaglandins E\textsubscript{1} and E\textsubscript{2} increased renal blood flow only with an intra-aortic infusion (85). A single passage of PGE\textsubscript{1} through the pulmonary circulation of the cat and dog caused a 73 to 99 per cent loss of its vasodilator activity while there was only a 0 to 30 per cent loss of vasodilator activity of the PGA's after a single passage through the lung (62). The prostaglandins are also metabolized to a great extent in the liver. A single passage of PGE\textsubscript{1}, A\textsubscript{1} and A\textsubscript{2} through the hepatic portal circulation of the cat caused a 55 to 59 per cent loss of their vasodilator activity (62). In the rat liver a single injection of \textsuperscript{14}C PGE\textsubscript{1} showed that the liver removed 89 to 95 per cent of the circulating PGE\textsubscript{1} on a single passage. The prostaglandin breakdown products are excreted into the bile and venous effluent (26). In addition, the prostaglandins are metabolized at other sites and are excreted into the urine as 5, 10 diketo, 7-hydroxy tetranor prostanel, 16-dioic acid (89). See Figure 18 for prostaglandin breakdown.
Figure 18. Degradation of prostaglandins E$_2$ and F$_2$α in man (79).
PROSTAGLANDIN BREAKDOWN IN MAN

$\text{PG E}_2$  $\text{PG F}_2\alpha$

- PG DEHYDROGENASE
- PG $\Delta^3$ REDUCTASE
- $\beta$-OXIDATION
- $\omega$-OXIDATION
- $\omega$-HYDROXYLATION

OTHER METABOLITES
Prostaglandin Inhibitors

The synthesis of prostaglandins is inhibited by indomethacin, aspirin, naproxen and meclofenamic acid \((7^4, 7^8, 8^1, 8^9, 9^4, 12^5)\) which inhibit prostaglandin synthetase. Meclofenamic acid blocks the vagal action of \(\text{PGF}_{2\alpha}\) in the cat heart \((7^8)\), the systemic vasodepressor response of \(\text{PGF}_{2\alpha}\) in the rabbit and the synthesis of prostaglandin in the canine heart and the increase in coronary blood flow caused by the prostaglandins \((7^4)\). Meclofenamic acid does not block most hemodynamic actions of \(\text{PGF}_{2\alpha}\) in the cat \((7^8)\) and does not block the vasodepressor response of \(\text{PGE}_1\) in the rabbit \((8^1)\). Indomethacin blocks the synthesis of \(\text{PGE}_2\) from arachidonic acid in the bovine seminal vesicle \((12^5)\). It also blocks prostaglandin synthesis in the canine heart which causes an increase in coronary blood flow, but it does not block reactive hyperemia of the coronary system in the dog heart \((7^4, 9^4)\).

Other prostaglandin inhibitors include polyphloretin phosphate (PPP), 7-oxa-13, 4 prostynoic acid (OPA), SC-19220 (a dibenzoxazepine derivative), 7-oxo-\(\text{PGE}_1\), 7-oxo-\(\text{PGF}_{1\alpha}\), morphine sulfate, 15-R-\(\text{PGE}_1\) and \(\text{PGB}_1\). SC-19220 and morphine sulfate inhibit the smooth muscle stimulating effect of \(\text{PGE}_1\) in the guinea pig ileum \((9^7)\). SC-19220, PPP and OPA also competitively inhibit the smooth muscle stimulating action of \(\text{PGE}_1\), \(\text{PGE}_2\) and \(\text{PGF}_{2\alpha}\) in dogs but not the vascular actions of \(\text{PGE}_1\), \(\text{PGE}_2\), \(\text{PGA}_1\) or \(\text{PGF}_{2\alpha}\) \((9^2)\). PPP abolishes the contractions of the jird colon caused by \(\text{PGF}_{1\alpha}\) and \(\text{PGF}_{2\alpha}\) but not those caused by \(\text{PGE}_1\) or \(\text{PGE}_2\) \((3^2)\).

In the rabbit PPP blocks the actions of \(\text{PGE}_1\) and \(\text{PGF}_{2\alpha}\) on isolated smooth muscle but not their actions on the cardiovascular system \((8^1)\).
7-oxo-PGE\textsubscript{1} and 7-oxo-PGF\textsubscript{1\alpha} are competitive inhibitors of PGE\textsubscript{1} in the smooth muscle of the gerbil colon. 15-R-PGE\textsubscript{1} and PGB\textsubscript{1} noncompetitively inhibit the enzymatic action of 15-hydroxy-prostaglandin dehydrogenase on PGE\textsubscript{1} but do not inhibit the vasodilator action of PGE\textsubscript{1} in the dog. It appears that there is no specific agent available which antagonizes the cardiovascular actions of the prostaglandins \cite{97}.

**Effects of Prostaglandins on the Gastrointestinal Tract**

The gastrointestinal effects of PGE\textsubscript{1}, PGE\textsubscript{2}, PGF\textsubscript{2\alpha} and to a lesser extent PGA\textsubscript{1} and PGF\textsubscript{1\alpha} have been studied. Prostaglandins have been isolated from gastrointestinal smooth muscle and mucosa and from the pancreas of animals and man. They have also been detected in animal but not in human liver. Human tissues have yielded mainly PGE\textsubscript{2}, but both PGE\textsubscript{2} and PGF\textsubscript{2\alpha} have been found in animals. Spontaneous release of prostaglandins have been reported in both in vitro and in vivo gastrointestinal preparations. Stimuli which increase the rate at which prostaglandins are released from the gastrointestinal tract include acetylcholine, DMPP, transmural and vagal electrical stimulation, gastrin, pentagastrin, histamine, theophylline, cyclic AMP, arachidonic acid and phospholipase A. Perfusion of the isolated rat liver with glucagon also causes the release of PGA\textsubscript{1} \cite{61, 133}.

PGE\textsubscript{1} and PGE\textsubscript{2}.

Since prostaglandins occur naturally in the gut wall, they may be involved in the normal motor activity of the gastrointestinal tract.
Studies in vitro have shown that in general human and animal longitudinal muscle from both the small and large intestine is contracted by the PGE's, while circular muscle is relaxed (4, 133). In the guinea pig and human ileum both PGE₁ and E₂ contracted the isolated longitudinal muscle and relaxed the circular muscle (110). Studies in vivo on gastrointestinal motility are generally in agreement with the in vitro observations. The PGE's in animal experiments have been found to inhibit jejunal and antral motility while they stimulate ileal motility (133). In the cat PGE₁, however, inhibited the motility of the ileum, an effect which was not abolished by alpha-adrenergic receptor blockade (127).

The PGE's given parenterally or orally reduce the volume of acid and pepsinogen secreted by the stomach in both conscious and anesthetized animals by a mechanism which, as yet, is not understood. PGE₁ inhibits gastric acid secretion stimulated by histamine or gastrin in rats, dogs and bullfrogs but not in humans (4, 22, 61, 133). The PGE's are powerful vasoactive agents which dilate the gastric blood vessels in fasting animals; however, during the inhibition of acid secretion with the PGE's gastric blood flow is reduced. The reduction in blood flow may be the result of the inhibition of acid secretion. PGE may modify cAMP levels to cause the decrease in acid secretion (133).

PGE₁ or PGE₂ has been administered for therapeutic abortion. One of the undesirable side effects which it often causes is diarrhea. Water and electrolyte transport across the intestinal mucosa seems to be altered. In vitro PGE₁ and PGE₂ inhibit Na⁺ absorption and stimulate Cl⁻ secretion in the isolated rabbit ileum. In dogs PGE₁ and PGE₂ in-
jected intra-arterially cause prompt secretion of water and electrolytes into jejunal loops. These effects can be prevented by pretreatment with polyphloretin phosphate in mice (133).

PGE's in the pancreas of animals inhibit secretin-stimulated fluid and electrolyte secretion and decrease pancreatic blood flow. In the dog PGE_1 causes an increase in pancreatic enzyme output which is not the consequence of release of pancreozymin (133).

PGF's

The prostaglandins F are very potent stimulants of intestinal smooth muscle. PGF_2\salpha contracts longitudinal smooth muscle from the large and small intestine of humans and animals, while it also contracts circular smooth muscle in vitro. PGF_2\salpha also contracts both longitudinal and circular gastric muscle (4, 61, 133). In vivo PGF_2\salpha increases both jejunal and ileal motility (133).

It has been observed that PGF_2\salpha more frequently causes diarrhea when used for therapeutic abortions than do the PGE's. It also inhibits Na^+ absorption and enhances Cl^- secretion in the rabbit ileal mucosa and causes secretion of water and electrolytes into canine jejunal loops (133).

PGF's do not affect pancreatic secretions, but PGF_2\salpha increases pancreatic vascular resistance in vitro (133).
PGA's and PGB's

Prostaglandins A and B have relatively weak activity on intestinal smooth muscle (61). PGA's cause only modest contractions of the small intestine. PGA₁ and PGA₂ given orally or parenterally, however, reduce gastric acid and pepsinogen secretion in both conscious and anesthetized animals. PGA's also dilate the gastric blood vessels in fasting animals, but during inhibition of acid secretion with PGA₁ or PGA₂ gastric blood flow is reduced. PGA's increase the secretion of water and electrolytes into canine jejunal loops, and may possibly be a cause of diarrhea. PGB₁ and PGB₂ have been found to increase the vascular resistance of the pancreas in vitro (133).

There is a great deal of evidence that the synthesis, release and breakdown of prostaglandins occur in the gastrointestinal tract tissues and that these prostaglandins may act as local regulators of gastrointestinal motility.

General Cardiovascular Effects of Prostaglandins

The prostaglandins may play an important role in cardiovascular regulation in health and disease. It is well established that PGE and PGA compounds are powerful vasodilators in many species of animals whereas PGF₂α is a moderately potent vasoconstrictor in dogs and rabbits. The PGE's and PGA's all decrease systemic arterial pressure.
It has been demonstrated that IV administration of \( \text{PGE}_1 \) decreases total peripheral resistance and systemic arterial pressure by directly vasodilating peripheral arteriolar smooth muscle in rats, cats, rabbits, guinea pigs, mice, dogs and man (97). It causes a transient increase in venous return in dogs (34) and decreases left atrial pressure, increases heart rate, pulmonary arterial pressure, cardiac output and myocardial contractile force (90). In dogs the depressor effect of intravenous \( \text{PGE}_1 \) is smaller than that of intra-arterial \( \text{PGE}_1 \) because \( \text{PGE}_1 \) is effectively inactivated by a single passage through the lungs (71, 97).

\( \text{PGE}_2 \) and \( \text{PGE}_3 \)

The hemodynamic effects of intravenous \( \text{PGE}_2 \) appear to be qualitatively and quantitatively similar to those of \( \text{PGE}_1 \) in dogs and man. \( \text{PGE}_2 \) decreases systemic arterial pressure and increases heart rate and myocardial contractile force in proportion to the dose given. \( \text{PGE}_3 \) injected intravenously also decreases systemic arterial pressure in rats, rabbits and cats. In general \( \text{PGE}_2 \) is slightly more active than \( \text{PGE}_1 \) on the cardiovascular system, whereas \( \text{PGE}_3 \) is less active than either \( \text{PGE}_1 \) or \( \text{PGE}_2 \) (97).
PGA₁ and PGA₂

The hemodynamic effects of the prostaglandins A are qualitatively similar to those of the prostaglandins E in the dog and rat (97). PGA compounds directly vasodilate peripheral arteriolar smooth muscle. PGA₁ causes a significant fall in systemic arterial pressure and total peripheral resistance in conscious rats and dogs, anesthetized rats, dogs, cats and rabbits (3, 59, 77, 90, 97) and humans (134). It increases heart rate, pulmonary arterial pressure, cardiac output and myocardial contractile force (59, 90, 97). In conscious dogs it also increases coronary flow and decreases coronary resistance; this effect was not blocked by administering propranolol, a beta adrenergic blocking agent (59). In man PGA₁ administered intravenously increases femoral artery flow, coronary and popliteal arterial blood flows (56). Given intravenously to dogs the PGA's are equipotent but more potent than the PGE's in affecting cardiovascular hemodynamics. PGE's are inactivated in one passage through the lungs whereas the PGA's are not. The PGA's are poorer substrates for 15-hydroxy-prostaglandin dehydrogenase than are the PGE's (97).

PGF₁₀ and PGF₂₀

Both PGF₁₀ and PGF₂₀ exert a mild to moderate vasodilator action in cats and rabbits and a vasoconstrictor effect in rats and dogs. In dogs PGF₂₀ increases systemic arterial pressure, total peripheral resistance, cardiac output, heart rate and myocardial contractile force.
(34, 90, 97). PGF\textsubscript{2\alpha} seems to act as a vasoconstrictor increasing systemic venous return and thus cardiac output in dogs. PGF\textsubscript{2\alpha} also constricts regional arteries causing an increased total peripheral resistance and thus an increased systemic arterial pressure (97). The vasoconstriction in dogs seems to not be a result of alpha-adrenergic receptor stimulation, the release of catecholamines or sympathetic reflexes (83). PGF\textsubscript{2\alpha} causes pulmonary vasoconstriction in the bovine (1). In dogs the cardiovascular effects of PGF\textsubscript{2\alpha} are 5 times greater than those of PGF\textsubscript{1\alpha} (97).

\begin{itemize}
  \item PGB\textsubscript{1} and PGB\textsubscript{2}
\end{itemize}

PGB\textsubscript{2} is a potent vasoconstrictor in vitro in dogs. It, however, produces a dose dependent decrease in systemic arterial pressure in dogs (45) which may be due to the specific regional increase in renal blood flow it causes (35). PGB\textsubscript{1} also decreases systemic arterial pressure but is less potent than PGB\textsubscript{2} in this respect. Both decrease left ventricular pressure, heart rate and depress myocardial contractility. They increase pulmonary arterial pressure and cause vasoconstriction in the dog hind limb (35, 45).

Effects of Prostaglandins on the Splanchnic, Hepatic and Portal Circulations

The prostaglandins are potent vasoactive agents in the splanchnic circulation of most species. The prostaglandins A and E are usually vasodilators and the prostaglandins F and B are usually vasoconstrictors
of the mesenteric vascular bed. In anesthetized dogs intra-arterial injections of 0.6 to 1.2 μg of PGE₁, PGE₂, PGA₁ or PGA₂ markedly increase blood flow in the superior mesenteric artery (97, 112, 116, 129). Intravenous infusions of 0.01 to 1.0 μg/min of PGE₁ also increase mesenteric arterial flow in conscious dogs (97). In vitro strips of mesenteric arteries are relaxed by PGE₁, PGA₁, PGE₂ and PGF₂α. This effect was not abolished by alpha or beta-adrenergic blockade, atropine, LSD-25 or antihistamine (116).

In anesthetized dogs PGF₂α injected intra-arterially decreases blood flow in the superior mesenteric artery and increases vascular resistance (97). PGF₂α also increases mesenteric venous pressure in the rat (93). PGB₂ in vitro is a potent constrictor of cutaneous and mesenteric arterial and mesenteric venous smooth muscle in the dog (45).

In the rat pancreas infusions of PGA₂ (108), PGF₂α (107) and PGB₂ (45) cause an increase in pancreatic vascular resistance while PGE₂ infusion caused it to decrease (107).

Von Euler first showed that a crude prostaglandin preparation (mostly PGE₁) increased portal venous pressure and caused blanching of the liver in anesthetized cats. Pooling of blood in the portal circulation is thought to contribute to the decrease in systemic arterial pressure caused by the prostaglandins. In one study in dogs intra-arterial injections of PGE₁ caused dose dependent increases in hepatic arterial flow which were not blocked by propranolol. Given intravenously PGE₁ was found to transiently increase hepatic arterial and portal venous flows.
It was concluded that PGE₁ had a direct vasodilator effect on the hepatic arterial bed but no direct effect on the portal venous bed (43). Other studies disagree with this finding in the portal venous vascular bed. High concentrations of the prostaglandins PGE₁, PGE₂ and PGF₂α caused dose dependent contractions of the isolated rabbit portal vein (63). PGE₁ infused directly into the portal vein of dogs caused a biphasic vascular response - an initial increase in portal venous pressure followed by a decrease. The initial response was explained on the basis of reflex sympathetic stimulation and the response that followed as a direct vasodilation of the portal vein by PGE₁. PGF₂α injected directly into the portal vein caused portal vеноconstriction in the dog (97). The prostaglandins E may play a role in local control of hepatic blood flow, since prostaglandin E receptors specific for these prostaglandins have been found in the plasma membrane of the rat liver (100). Prostaglandins are inactivated in the liver by non-specific β and ω oxidation in most species (97).

Splenic Circulation

In dogs splenic nerve stimulation causes the release of PGE₂ into the splenic blood. This effect is blocked by phenoxybenzamine (25). Intra-arterial infusion of PGE₁ and PGE₂ into the isolated perfused dog spleen causes an increase in splenic arterial blood flow and splenic volume. These effects are not blocked by phenoxybenzamine or propranolol. Intra-arterial infusions of PGF₂α increase splenic arterial blood flow yet decrease splenic volume in dogs by causing constrict-
tion of splenic capacitance vessels. Infusions of PGF$_{1\alpha}$, PGA$_1$ or PGA$_2$ slightly increase splenic arterial blood flow and splenic volume (97).

**Gastric Circulation**

Both PGE$_1$ and PGA$_1$ given either intravenously or intra-arterially decrease gastric arterial perfusion pressure and gastric vascular resistance in dogs (91,97). PGE$_1$ decreases gastric mucosal blood flow in dogs. Since it decreases gastric resistance, it may cause a redistribution of gastric blood flow from the mucosa to other tissue layers of the stomach (91, 97). PGE$_2$ in the dog causes an increase in total gastric blood flow (111).

**Mechanisms of Action of the Prostaglandins**

**Hormonal Actions**

The biological actions of hormones are allegedly mediated by the second messenger, cyclic AMP, formed in the cell membrane by the enzyme adenylcylase. Various hormones which increase cyclic AMP levels also increase the release and concentration of prostaglandins in the tissues. Many recent studies indicate that a close relationship frequently exists between prostaglandins and cyclic AMP formation or action although the underlying mechanism including tissue specificity remains uncertain. As shown in Figure 19, PGE$_1$ stimulates the activity of adenylcylase which increases cyclic AMP in the heart, lung, bones, leucocytes, platelets, anterior pituitary gland, corpus luteum and the
Figure 19. Two possible mechanisms of action of the prostaglandins on the cyclic AMP system (79).
POSSIBLE MECHANISMS OF ACTION OF PROSTAGLANDIN ON THE CYCLIC AMP SYSTEM

HORMONES → PROSTAGLANDINS

\[ \text{receptor} \rightarrow \text{ADENYL CYCLASE} \rightarrow \text{ATP} \rightarrow \text{CYCLIC AMP} \]

BIOLICAL ACTIONS

PG SYNTHESIS

HORMONES PROSTAGLANDINS

PG SYNTHESIS

PGF_{2\alpha}, PGE_{2} (2nd messenger)

ADENYL CYCLASE

ATP → CYCLIC AMP (3rd messenger)

BIOLICAL ACTIONS
adrenals. PGE$_1$ inhibits the activity of adenylcyclase in the renal collecting tubules, medulla, toad bladder, stomach, adipose tissue and cerebellum (89).

Effects of Blocking Agents on Prostaglandin Actions

Many types of blocking agents have been used to determine the mechanism of action of the prostaglandins on the peripheral vasculature. It has been found that the vascular effects of the prostaglandins are not mediated by acetylcholine, biogenic amines or vasoactive peptides (89). The vasoactive properties of the prostaglandins E, especially PGE$_1$, are not blocked by alpha or beta-adrenergic receptor blockade, atropine, LSD-25, antihistamine, methyl sergide, vagotomy, anesthesia, tripelemamine, reserpine or ganglionic blocking agents in dogs (61, 97, 116). In cats PGE$_1$ induced tachycardia is completely blocked by Agentit and propranolol, but the reduced systemic arterial pressure effect is not (97). PGE$_1$ reduces the vasoconstrictor action of vaso-pressin or angiotensin in cats and rats (97).

The vasodilator effect of the prostaglandins A is not abolished by atropine, propranolol, antihistamine, LSD-25 or methyl sergide. The PGF$_{2\alpha}$ venoconstrictor action is not abolished by either phenoxybenzamine or methyl sergide (61, 116).
Prostaglandins and the Autonomic Nervous System

PGE₁ and PGE₂ inhibit norepinephrine and acetylcholine release at autonomic nerve endings. Consequently these prostaglandins reduce the vascular and cardiac actions induced by sympathetic or parasympathetic nerve stimulation. PGE₁ and PGE₂ appear to interfere with intraneuronal calcium transport, thereby inhibiting the cellular exocytosis of catecholamine or acetylcholine granules at the nerve endings. Prostaglandin synthetase inhibitors potentiate the vascular and cardiac effects induced by autonomic nerve stimulation. These observations confirm the assertion that autonomic nerve stimulation releases endogenous prostaglandins in amounts sufficient to exert an inhibitory action on transmitter release at the nerve endings. Thus it is suggested that the prostaglandins E may play a role in negative feedback control of autonomic neurotransmission (89). Catecholamine pressor responses have been blocked in the dog, rat and cat by PGE₁ or PGE₂ (68, 69, 97). PGA₁ also depresses the catecholamine pressor response in the dog hindpaw but is less potent than PGE₁ (69). PGE₁ inhibits parasympathetic neurotransmission in the rabbit heart (97).

PGF₂α, on the other hand, seems to enhance sympathetic adrenergic transmission by facilitating the release of transmitter from sympathetic nerve endings (68). This has been shown in the canine saphenous vein in which PGF₂α enhanced the venoconstrictor response to both sympathetic nerve stimulation and norepinephrine (80). PGF₂α infused into the vertebral artery of the dog caused an increase in heart rate and blood pressure attributed to the withdrawal of vagal tone to the
heart (80). Other prostaglandin groups have not been studied enough to warrant consideration of their actions on autonomic neurotransmission (97).
METHODS

GENERAL PREPARATION

Mongrel dogs averaging 20-25 kg in weight were anesthetized with an initial intravenous dose of sodium pentobarbital (30 mg/kg), and 65 to 130 mg doses were administered throughout the experiment as needed. An endotracheal tube was inserted, and if needed, the dog was ventilated with room air using a Harvard Apparatus dual phase control respirator pump (Model 613). The animals were hydrated with a constant intravenous drip of either 5 per cent dextrose in normal saline (Travenol) or 5 per cent dextrose in lactated Ringer's solution (Travenol) or Rheomacrodex (Dextran 40) in normal saline (Pharmacia Laboratories) throughout the experiment.

The right jugular vein and both femoral arteries and veins were isolated before the abdominal cavity was opened. All incisions were made using an electric cautery (Carolina Medical Electronics) to minimize bleeding. Excessive bleeding was stopped by ligating the vessels. When the experiments were concluded, the dogs were sacrificed with an intravenous dose of magnesium sulfate.
A diagonal incision was made in the right lower quadrant, ventral aspect, to expose the liver and splanchnic vessels of the upper abdomen. The splenic vasculature including the splenic artery was ligated and sectioned except for the splenic vein. The splenic nerves ensheathing the ligated splenic artery were stimulated with a Grass S48 stimulator set at 125 volts, 5 pulses per second. The spleen contracted, due to sympathetic nerve stimulation, returning its contents to the systemic circulation. The spleen was then removed by ligating the splenic vein. The common bile duct was isolated and an area of the portal vein was cleared of lymphatic tissue and sheath between the entry of the gastrosplenic vein and the gastroduodenal vein. The gastroduodenal artery was doubly ligated and sectioned between the origins of the right gastric artery and the most distal of the proper hepatic arteries. The area of the common hepatic artery between the origins of the left gastric artery and the most proximal of the hepatic arteries was cleared of all sheath, lymphatic tissue and nerves of the hepatic plexus. The cranial pancreaticoduodenal vein was isolated and cleared of all lymphatic and pancreatic tissue.

Sodium heparin (Organon, Inc.) was administered intravenously at a dose of 500 USP units per kilogram body weight before cannulating the vessels. A schematic diagram of the preparation is shown in Figure 20. The right femoral artery was cannulated toward the abdominal aorta with a polyethylene cannula (PE 350) in order to measure systemic
Figure 20. Diagram of the isolated, in-situ canine liver preparation.
arterial pressure (SAP in Figure 20). The right femoral vein was cannulated with a PE 350 catheter whose tip came to rest at the hilum of the liver in order to measure inferior vena cava pressure ($P_{IVC}$ in Figure 20). The left femoral vein was cannulated with a short PE 350 catheter used to infuse various agents intravenously (designated as IV inf. in Figure 20). In some experiments involving the prostaglandins, infusion was directly into the liver, either by way of the hepatic arterial or the portal venous inflow circuit. The jugular vein was cannulated with a short PE 390 catheter attached to a plastic reservoir with a length of silastic tubing. The splenic vein was cannulated with a short polyethylene catheter attached to a Y-connector one end of which was connected to the jugular vein cannula circuit with silastic tubing. In this manner splanchnic venous outflow was shunted via the splenic vein into the jugular vein when the portal vein was ligated. This procedure prevented splanchnic pooling of blood. Next the portal vein was ligated and cannulated with PE 430 tubing. The portal cannula was connected to the other end of the splenic Y-connector with silastic tubing (1/4 inch I.D.). Clamp $C_1$ was closed and clamp $C_2$ opened so that all splanchnic venous outflow was then diverted into the portal vein (see Figure 20). When clamp $C_2$ was closed and $C_1$ opened, splanchnic flow was diverted into the jugular vein. An electromagnetic blood flow probe (In Vivo Metric Model H-1C, 7 mm diameter) was inserted into the portal venous perfusion circuit in order to measure portal venous flow ($F_{PV}$ in Figure 20). Portal venous pressure was measured by cannulating the pancreaticoduodenal vein with a polyethylene (PE 350) catheter.
The left femoral artery was cannulated with PE 350 tubing attached to silastic tubing and used to perfuse the hepatic artery which was cannulated with a PE 280 catheter. Hepatic arterial pressure ($P_{HA}$ in Figure 20) was measured via a T-tube placed in the hepatic arterial perfusion circuit. Hepatic arterial blood flow ($F_{HA}$ in Figure 20) was measured with an electromagnetic blood flow probe (In Vivo Metric, 3 mm diameter) placed in the extracorporeal circuit. All pressures were measured with Statham P23Ac transducers. Blood flows were measured using a four channel Biotronex electromagnetic flowmeter (Model BL-410). Blood pressures and flows were recorded using a Gilson macropolygraph. Vascular resistances were calculated in peripheral resistance units (mm Hg/ml/min/100 gms liver tissue). In these experiments both hepatic arterial ($R_{HA}$) and portal venous ($R_{PV}$) resistances were calculated.

$$R_{HA} = \frac{P_{HA} - P_{IVC}}{F_{HA}}$$

$$R_{PV} = \frac{P_{PV} - P_{IVC}}{F_{PV}}$$

The cystic duct was ligated and the common bile duct was cannulated in order to collect bile. Bile was allowed to drain to the exterior throughout the experiment. Bile flow values as given, represent the mean rate of flow during the immediately preceding 5 or 10 minute interval.
A midline abdominal incision was made in each dog to expose the small intestine. The terminal portion of the cranial (or superior) mesenteric artery was cleared of all nerves, lymphatic tissue and sheath, and several jejunal arteries were ligated and sectioned in order to expose a length of artery suitable for cannulation. The cranial mesenteric vein was also cleared of all tissue, and several jejunal veins were also ligated to expose a length of vein for cannulation. The section of small intestine served by the ligated jejunal arteries and veins was resected and removed to prevent the release of toxic products from the ischemic tissue. A length of ileum averaging 150 to 200 grams was resected and a plastic tube tied in each end to facilitate drainage and prevent bleeding. The terminal jejunum was also anastomosed to the terminal ileum with another plastic tube.

The dogs received a 500 USP units/kg dose of sodium heparin (Organon, Inc.) as an anticoagulant before cannulation. A schematic diagram of the preparation is shown in Figure 21. A femoral artery was cannulated with a PE 350 catheter in order to measure systemic arterial pressure (SAP in Figure 21). The other femoral artery was cannulated and used to perfuse the isolated length of ileum. The arterial perfusion circuit, made of silastic tubing, contained an electromagnetic blood flow probe (In Vivo Metrics, 3 mm diameter) used to measure the intestinal artery blood flow ($F_A$ in Figure 21). Intestinal artery perfusion pressure ($P_A$ from Figure 21) was also measured from a T-
Figure 21. Diagram of the isolated canine small intestine preparation.
connector in the arterial perfusion circuit. The mesenteric vein was cannulated and the venous outflow was allowed to drain via silastic tubing into a plastic reservoir. The latter was connected to a polyethylene cannula directed centrally in a jugular vein. Venous inflow to the jugular vein was controlled by adjusting the clamp (in Figure 21). Intestinal venous pressure \( P_v \) in Figure 21 was measured from a T-connector in the venous outflow circuit. All pressures were measured with Statham P23Ac transducers and blood flow with a Biotronex electromagnetic flowmeter (Model BL-410). Recording was with a Gilson macro-polygraph. The resected length of isolated ileum rested on a plastic platform and was covered with gauze soaked in normal saline to prevent dehydration. The preparation was kept warm with a heat lamp. The vascular resistance \( R_T \) of the resected ileal preparation was calculated in peripheral resistance units (mm Hg/ml/min/100 grams gut tissue).

\[
R_T = \frac{P_A - P_V}{F_A}
\]

PREPARATION AND INFUSION OF COMPOUNDS

Synthetic gastrin pentapeptide (Calbiochem, B grade) was infused via the femoral vein in both liver and small intestine preparations. Before infusion it was dissolved in 0.9 per cent saline to which a small amount of propylene glycol had been added to promote dissolving. Before infusion the stomach at the pylorus was clamped to
prevent flow of acid contents into the duodenum. Pentagastrin induced acid secretion was thus prevented from causing the release of secretin from the duodenal mucosa. Pentagastrin was infused at the rate of 10 µg/kg/hr for one hour in the liver experiments and at the rate of 5 µg/kg/hr in the small intestine experiments.

Secretin (Calbiochem) was dissolved in 0.9 per cent saline and infused via the femoral vein in both groups of experiments at the rate of 4 U/min for 20 minutes.

Pancreozymin (Calbiochem, B Grade) was only studied in the liver preparation. It was dissolved in 0.9 per cent saline and infused via the femoral vein at the rate of 2.73 U/min for 30 minutes.

The bile salts were infused via the femoral vein in both liver and small intestine experiments. Sodium taurocholate (Calbiochem, A Grade) was dissolved in 0.9 per cent saline and infused at the rate of 8.1 mg/min in both groups of experiments. Sodium dehydrocholate (Endo Laboratories) was diluted in 0.9 per cent saline and infused at the rate of 30.6 mg/min for 60 minutes.

Prostaglandins were obtained courtesy of the Upjohn Company. These were made into a 1 mg/ml stock solution, buffered between pH 6 and 7.5 for maximum stability with sodium carbonate solution. The stock solution also contained 10 per cent ethanol. The solution was frozen when not in use. The prostaglandin stock solution was diluted in 0.9 per cent saline before infusion. Prostaglandin A₁ was infused at the rate of 2 µg/kg/hr for 30 minutes via the femoral vein in the liver experiments. In the small intestine experiments it was infused directly
into the mesenteric arterial vasculature at the rate of 2 µg/kg/hr for 30 minutes. Prostaglandin B\textsubscript{1} was also infused intra-arterially directly into the small intestine at the rate of 80 µg/kg/hr for 30 minutes. In the liver experiments it was infused at the rate of 80 µg/kg/hr for 15 minutes into the portal vein and then for 15 minutes into the hepatic artery. All infusions of these compounds were made using a Harvard constant rate perfusion pump.

**STATISTICAL TREATMENT OF DATA**

All data are expressed as the mean ± one standard error of the mean (S.E.). Each experiment, in fact, each infusion, served as its own control. Experimental values during the infusion were compared with the control value existing during the 10 minute period immediately preceding the onset of the infusion in each case. The t-test was then applied to the mean of the differences between these paired values, experimental minus control. This was calculated on the basis of the equations given below.

\[x = \text{control value}\]

\[x' = \text{experimental value}\]

\[d = x' - x = \text{difference between values}\]

\[\bar{d} = \text{mean of the differences between values}\]

\[s_d = \text{standard error of the difference}\]

\[n-1 = \text{degrees of freedom, one less than the number of pairs.}\]
Changes from control which are statistically significant by this method are so designated in the text of the Results section. The criterion chosen for defining this was a p value of 0.05 or less.

\[ s = \sqrt{\frac{\sum (d - \bar{d})^2}{n-1}} \]

\[ \frac{\bar{d}}{s_d} = \frac{s}{\sqrt{n}} \]

\[ t = \frac{\bar{d}}{s_d} \]
RESULTS

PENTAGASTRIN

Synthetic gastrin pentapeptide was given by intravenous infusion at a rate of 10 μg/kg/hr for 60 minutes in a series of 9 liver experiments. The data are summarized in Figure 22. There was a slight but statistically significant ($p > 0.02$) transient increase in bile flow of about 17 per cent. It increased from a control value of $0.65 \pm 0.10$ (S.E.) to $0.76 \pm 0.11$ (S.E.) ml/hr/100 grams by 20 minutes after the start of the infusion. By 50 minutes after the start of the infusion, bile flow had essentially returned to the control level. Also after about 20 to 30 minutes of infusion, liver blood flow generally increased and resistance decreased. There was an 8 per cent increase in hepatic arterial flow by 30 minutes after the start of the infusion, while hepatic arterial resistance significantly ($p > 0.02$) decreased by about 15 per cent, 20 to 40 minutes after the start of the infusion. Portal venous flow increased significantly from $60.3 \pm 9.4$ (S.E.) to $68.5 \pm 10.5$ (S.E.) ml/min/100 grams, about 14 per cent, after 10 minutes of infusion. Intrahepatic portal venous resistance decreased by 15 per cent by the end of the infusion period. There was no change in systemic arterial pressure. Figure 23 shows the effects on total liver blood flow and bile flow at 30 and 60 minutes after the onset of pentagastrin infusion.
Figure 22. Effects of the intravenous infusion of pentagastrin (10 μg/kg/hr) on hepatic bile flow, hepatic arterial blood flow ($F_{HA}$) and resistance ($R_{HA}$), portal venous blood flow ($F_{PV}$), intrahepatic portal venous resistance ($R_{PV}$) and systemic arterial pressure ($P_A$).
Figure 23. Effects of intravenous infusion of pentagastrin on total liver blood flow and bile flow.
In a series of 5 small intestine experiments, pentagastrin was infused intravenously at the rate of 5 μg/kg/hr for 60 minutes. The results are given in Figure 24. Mean changes in blood flow and resistance were not statistically significant, nor was the slight 4 per cent decrease in systemic arterial pressure.

SECRETIN

Intravenous infusion of secretin at a rate of 4 units/min for a period of 20 minutes was performed in a series of 11 liver experiments. As shown in Figure 25, this resulted in an immediate choleric response. The increase in bile flow was highly significant (p < 0.01) being about 2.6 times that seen during the control period. It increased from $0.7 \pm 0.1$ (S.E.) to $1.8 \pm 0.1$ (S.E.) ml/hr/100 grams by 20 minutes after the start of the infusion. Portal venous flow increased transiently by 5 per cent after 10 minutes of infusion; however, there was no change in hepatic arterial flow, hepatic arterial resistance, intrahepatic portal venous resistance or systemic arterial pressure as shown in Figure 25. Figure 26 shows that while bile flow increased greatly, total liver blood flow showed little or no change during secretin infusion.

Secretin was also infused intravenously at the rate of 4 units/min for 20 minutes in a series of 8 small intestine experiments. Small intestine blood flow increased significantly (p < 0.02) by 10 min-
Figure 24. Effects of intravenous infusion of pentagastrin (5 µg/kg/hr) on small intestine blood flow and vascular resistance.
Figure 25. Effects of intravenous infusion of secretin (4 units/min) on liver blood flow, resistance, bile flow and systemic arterial pressure.
Figure 26. Effects of intravenous infusion of secretin on total liver blood flow and bile flow.
utes after the start of the infusion. Flow increased from a control value of \(34.7 \pm 6.0 \text{(S.E.)}\) to \(38.4 \pm 6.0 \text{(S.E.)}\) ml/min/100 grams by 10 minutes after the start of the infusion. Small intestine vascular resistance decreased significantly \((p < 0.01)\) by 10 to 20 minutes after the start of the infusion. After 10 minutes of infusion, resistance had decreased from \(3.27 \pm 0.54 \text{(S.E.)}\) during the control period to \(2.82 \pm 0.51 \text{(S.E.)}\) mm Hg/ml/min/100 grams. These results are shown in Figure 27. There was only a slight 1 per cent decrease in systemic arterial pressure by 20 minutes after the start of the infusion.

**PANCREOZYMIN**

In a series of 14 dog liver preparations, pancreozymin was infused intravenously at the rate of 2.73 units/min for a period of 30 minutes. The results are given in Figure 28. There was little increase in bile flow during the first 10 minutes of infusion; however, after 20 minutes of infusion, bile flow had increased significantly \((p < 0.01)\) by 33 per cent over control values. After 30 minutes of infusion the mean rate of bile flow was over 1.7 times that seen during the control period. It increased from a value of \(0.75 \pm 0.07 \text{(S.E.)}\) during the control period to \(1.29 \pm 0.10 \text{(S.E.)}\) ml/hr/100 grams after 30 minutes of infusion. Portal venous flow transiently increased by over 5 per cent after 10 minutes of infusion. Systemic arterial pressure decreased significantly \((p < 0.01)\) from \(121 \pm 5 \text{(S.E.)}\) to
Figure 27. Effects of intravenous infusion of secretin (4 units/min) on small intestine blood flow and resistance.
Figure 28. Effects of intravenous infusion of pancreozymin (2.73 units/min) on liver blood flow, resistance, bile flow and systemic arterial pressure.
113 ± 5 (S.E.) mm Hg, a 7 per cent decrease, by the end of the infusion period. However, there was no change in hepatic arterial flow, hepatic arterial resistance or intrahepatic portal venous resistance. Figure 29 shows that although there was a marked increase in bile flow, there was no change in total hepatic blood flow during the intravenous infusion of pancreozymin.

SODIUM DEHYDROCHOLATE

A group of 15 dogs received femoral venous infusions of the synthetic, non-conjugated, oxidized bile acid product sodium dehydrocholate (3, 7, 12-triketocholanolate) at a rate of 30.6 mg/min for a period of 60 minutes. Figure 30 shows the effects of the infusion on hepatic bile flow and hemodynamics. Bile flow increased significantly (p < 0.01). After 10 minutes of infusion, the value was 1.2 times that of the control. It continued to rise until by the end of the infusion period, the rate had increased from a value of 1.3 ± 0.2 (S.E.) to 5.3 ± 0.5 (S.E.) ml/hr/100 grams, an increase nearly 4 times that seen during the control period. There was little or no change in hepatic arterial flow; however, hepatic arterial resistance declined significantly (p < 0.01) by over 8 per cent after 30 minutes of infusion and continued to decrease until by the end of the infusion period, it had dropped from a control value of 4.02 ± 0.44 (S.E.) to 3.49 ± 0.30 (S.E.) mm Hg/ml/min/100 grams, a 13 per cent decrease. Portal venous flow de-
Figure 29. Effects of intravenous infusion of pancreozymin on total liver blood flow and bile flow.
Figure 30. Effects of intravenous infusion of sodium dehydrocholate (30.6 mg/min) on liver blood flow, resistance, bile flow and systemic arterial pressure.
creased slightly, by about 13 per cent, after 50 minutes of infusion, while intrahepatic portal venous resistance increased by about 23 per cent. Systemic arterial pressure decreased significantly ($p > 0.02$), by about 7 per cent, after 20 minutes of infusion and continued to decline until by the end of the infusion period, it had decreased from a control value of $120 \pm 6$ (S.E.) to $106 \pm 6$ (S.E.) mm Hg (a 12 per cent decrease). As shown in Figure 31, there was a marked increase in bile flow, while total hepatic blood flow actually decreased slightly during the infusion period.

The effects of the same infusion of sodium dehydrocholate on small intestine hemodynamics was studied in another 8 experiments. The data are shown in Figure 32. Small intestine blood flow decreased and vascular resistance increased transiently after 10 to 20 minutes of infusion; however, both returned to near their control values by the end of the infusion period. Ten minutes after the start of the infusion, blood flow decreased by 11 per cent, from a control value of $28.5 \pm 5.3$ (S.E.) to $25.5 \pm 4.6$ (S.E.) ml/min/100 grams, and vascular resistance increased by 8 per cent, from a control value of $4.38 \pm 0.73$ (S.E.) to $4.76 \pm 0.75$ (S.E.) mm Hg/ml/min/100 grams. Systemic arterial pressure decreased significantly ($p < 0.05$) after 10 minutes of infusion and continued to decline throughout the infusion period from a control value of $128 \pm 4$ (S.E.) to a value of $107 \pm 12$ (S.E.) mm Hg by the end of the infusion period (a 15 per cent decrease).
Figure 31. Effects of intravenous infusion of sodium dehydrocholate on total liver blood flow and bile flow.
Figure 32. Effects of intravenous infusion of sodium dehydrocholate (30.6 mg/min) on small intestine blood flow and resistance.
SODIUM TAUCOCHOLATE

In another 8 liver experiments, the non-oxidized conjugated bile salt sodium taurocholate (a taurine conjugate of sodium cholate; 3, 7, 12-trihydroxycholanate) was infused via the femoral vein for 60 minutes at the rate of 8.1 mg/minute. The results are shown in Figure 33. Bile flow increased significantly \((p < 0.01)\), by over 18 per cent, after 10 minutes of infusion. After 50 minutes of infusion, the rate had risen from a control value of \(1.24 \pm 0.15\) (S.E.) to \(2.65 \pm 0.16\) (S.E.) ml/hr/100 grams, more than a two-fold increase. Throughout the infusion period there was little or no change in hepatic arterial flow or resistance. During the infusion portal venous flow significantly decreased \((p > 0.01)\), and intrahepatic portal venous resistance significantly increased \((p > 0.01)\). Portal venous flow decreased by nearly 12 per cent from a control value of \(89.6 \pm 10.0\) (S.E.) to a value of \(79.1 \pm 9.7\) (S.E.) ml/min/100 grams by the end of the infusion period. Also by the end of the infusion period, portal venous resistance rose nearly 15 per cent, from a control value of \(0.064 \pm 0.007\) (S.E.) to a value of \(0.073 \pm 0.007\) (S.E.) mm Hg/ml/min/100 grams. Systemic arterial pressure declined slightly until by the end of the infusion it was 4 per cent below the control value. Figure 34 shows that bile flow significantly increased, while total hepatic blood flow slightly decreased.

In a series of 6 small intestine experiments, sodium taurocholate infused intravenously at the same rate and time period as in
Figure 33. Effects of intravenous infusion of sodium taurocholate (8.1 mg/min) on liver blood flow, resistance, bile flow and systemic arterial pressure.
Figure 34. Effects of intravenous infusion of sodium taurocholate on total liver blood flow and bile flow.
the liver experiments, produced no significant change in small intestine blood flow or vascular resistance. The results are shown in Figure 35. However, the mean value for resistance did tend to increase by 15 per cent after 50 minutes of infusion. Systemic arterial pressure decreased by 4 per cent, from a control value of 126 ± 7 (S.E.) to a value of 121 ± 5 (S.E.) mm Hg by the end of the infusion period.

**PROSTAGLANDIN A₁**

In a series of 11 liver experiments prostaglandin A₁ (PGA₁) was infused via the femoral vein at the rate of 2 μg/kg/hr for 30 minutes. The results are shown in Figure 36. Bile flow dropped continuously throughout the infusion period, but the decline was only significant (p > 0.01) after 20 minutes of infusion when it decreased by more than 10 per cent. By the end of the infusion period, the rate had decreased by 16 per cent from a control value of 1.28 ± 0.27 (S.E.) to 1.07 ± 0.23 (S.E.) ml/hr/100 grams. Hepatic arterial flow slightly decreased throughout the infusion period until after 30 minutes it was nearly 12 per cent below the control value. Hepatic arterial resistance remained essentially the same as the control throughout the infusion period, except at 5 minutes after the infusion was started when it transiently decreased significantly (p > 0.02) by nearly 6 per cent. Portal venous flow decreased significantly (p > 0.02) by nearly 11 per cent after 10 minutes of infusion and continued to decline until by the
Figure 35. Effects of intravenous infusion of sodium taurocholate (8.1 mg/min) on small intestine blood flow and resistance.
Figure 36. Effects of intravenous infusion of prostaglandin A₁ (2 μg/kg/hr) on liver blood flow, resistance, bile flow and systemic arterial pressure.
end of the infusion period it had decreased by 16 per cent, from a control value of $88.0 \pm 15.7$ (S.E.) to $73.6 \pm 12.2$ (S.E.) ml/min/100 grams. Intrahepatic portal venous resistance slightly increased throughout the infusion period until after 30 minutes of infusion it was nearly 15 per cent above the control value. Systemic arterial pressure declined immediately after the start of the infusion and continued to decrease throughout the infusion period. The 9 per cent decrease in pressure after 5 minutes of infusion was significant ($p < 0.01$). By the end of the infusion period, pressure had decreased from a control value of $127 \pm 6$ (S.E.) to $107 \pm 6$ (S.E.) mm Hg, a 16 per cent decrease. In Figure 37 it is again shown that both bile flow and total hepatic blood flow decreased continuously throughout the infusion of PGA₁.

In a series of 9 experiments, PGA₁ was infused intra-arterially directly into the small intestine segment at a rate of 2 μg/kg/hr for 30 minutes. The effects on small intestine hemodynamics are shown in Figure 38. Blood flow increased transiently and peaked after one minute of infusion, declining thereafter to a level which was significantly ($p < 0.01$) below the control value after 20 minutes of infusion. The transient 57 per cent increase in flow, which rose from a control value of $21.6 \pm 2.4$ (S.E.) to $34.0 \pm 5.1$ (S.E.) ml/min/100 grams after one minute of infusion, was statistically significant ($p > 0.02$). The subsequent decline in flow continued until it reached a value of $17.1 \pm 1.9$ (S.E.) after 20 minutes of infusion, a 21 per cent decrease from the control value. An immediate decrease in vascular resistance also reflected the transient vasodilator response seen after the onset
Figure 37. Effects of intravenous infusion of prostaglandin A₁ on total liver blood flow and bile flow.
Figure 38. Effects of intra-arterial infusion of prostaglandin $A_1$ (2 μg/kg/hr) on small intestine blood flow and resistance.
of PGA\textsubscript{1} infusion. After one minute of infusion, resistance decreased from a control value of \(4.68 \pm 0.52\) (S.E.) to \(2.89 \pm 0.37\) (S.E.) mm Hg/ml/min/100 grams, a significant (\(p > 0.01\)) decrease of over 38 per cent. Thereafter resistance increased until by the end of the infusion period, it had returned to slightly above the control value. Systemic arterial pressure decreased continuously throughout the infusion until by 10 minutes it had significantly (\(p > 0.01\)) declined by more than 10 per cent. By the end of the infusion period pressure had decreased by 14 per cent, from a control value of \(125 \pm 3\) (S.E.) to \(108 \pm 3\) (S.E.) mm Hg.

In another series of 8 small intestine experiments the dose response to PGA\textsubscript{1} was tested, and beta-adrenergic receptors were blocked by Sotalol to determine if the initial transient vasodilation was due to beta stimulation. See Table 2 and 3 for a summary of the data. PGA\textsubscript{1} was first infused intra-arterially at the rate of 1 \(\mu g/kg/hr\) for 20 minutes. There was a transient 22 per cent increase in blood flow and a 21 per cent decrease in resistance after one minute of infusion. By 10 minutes after the start of the infusion, blood flow and resistance had returned to near control levels. After a 20 minute recovery period PGA\textsubscript{1} was again infused intra-arterially, this time at the rate of 2 \(\mu g/kg/hour\). Blood flow increased transiently by nearly 32 per cent over the control level, and resistance decreased by 32 per cent. Blood flow and resistance did not return to control levels until the end of the infusion period. At the 2 \(\mu g/kg/hr\) dose of PGA\textsubscript{1}, the increase in blood flow was significantly greater after 1 minute of infusion (43 per cent greater) than it was with the 1 \(\mu g/kg/hr\) dose. The resistance
Table 2. Effects of intra-arterial infusion of prostaglandin A₁ (1 µg/kg/hr and 2 µg/kg/hr) on small intestine blood flow and resistance before and after Sotalol.
Table 2

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<th>Resistance (mm Hg/ml/min/100 grams)</th>
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<td>--</td>
<td>4.30 ±0.82</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>--</td>
<td>4.43 ±0.75</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>--</td>
<td>4.30 ±0.82</td>
</tr>
<tr>
<td>PGA₁ - 2 ug/kg/hr</td>
<td>0</td>
<td>22.9 ±3.7</td>
<td>4.48 ±0.79</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>32.0 ±4.1</td>
<td>2.89 ±0.43</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>28.0 ±4.4</td>
<td>3.53 ±6.50</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>24.8 ±3.6</td>
<td>3.91 ±7.40</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>24.5 ±3.6</td>
<td>3.97 ±7.60</td>
</tr>
</tbody>
</table>
Table 3. Effects of intra-arterial infusion of prostaglandin A₁ (1 μg/kg/hr and 2 μg/kg/hr) on per cent change in small intestine blood flow and resistance before and after Sotalol.
Table 3

<table>
<thead>
<tr>
<th>Time-Minutes</th>
<th>PGA₁ - 1 ug/kg/hr</th>
<th>PGA₁ - 2 ug/kg/hr</th>
<th>PGA₂ - 2 ug/kg/hr after Sotalol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infused</td>
<td>1</td>
<td>2</td>
<td>10</td>
</tr>
<tr>
<td>PGA₁ - 1 ug/kg/hr</td>
<td>+22.3</td>
<td>+12.2</td>
<td>-0.7</td>
</tr>
<tr>
<td>PGA₁ - 2 ug/kg/hr</td>
<td>+31.9*</td>
<td>+16.5*</td>
<td>+3.3</td>
</tr>
<tr>
<td>PGA₂ - 2 ug/kg/hr after Sotalol</td>
<td>+39.7</td>
<td>+22.2</td>
<td>+8.3</td>
</tr>
</tbody>
</table>

*Significantly different from the immediately preceding value at the same time period (p < 0.05).
decrease after one minute of infusion was significantly greater (by 46 per cent) at the 2 µg/kg/hr dose than at the 1 µg/kg/hr dose. By the end of the infusion period, the blood flow increase at the 2 µg/kg/hr dose was still relatively greater (over 6 per cent) than that at the 1 µg/kg/hr dose.

Twenty minutes after the completion of the 2 µg/kg/hr dose of PGA₁, Sotalol was infused intravenously at the rate of 19.1 mg/min for 20 minutes (total dose ca. 20 mg/kg). Following another 20 minute interval, the infusion of PGA₁ was repeated at the rate of 2 µg/kg/hr for 20 minutes. The transient increase in blood flow 1 minute after the infusion was started, was even greater than that seen with the 2 µg/kg/hr dose before Sotalol was administered. The decrease in resistance was also greater. However, these changes were not significantly different from those seen before the infusion of Sotalol. The transient increase in blood flow is thus not likely due to beta-adrenergic receptor stimulation. During the infusions of PGA₁ in this series of experiments systemic arterial pressure did not change significantly.

PROSTAGLANDIN B₁

In a series of 11 liver experiments, prostaglandin B₁ (PGB₁) was infused directly into the liver, first via the portal vein at a rate of 80 µg/kg/hr for 15 minutes, and then after a 15 minute recovery period by way of the hepatic artery at the same infusion rate. The
results are shown in Figures 39 and 40. No choleretic effect was seen after the infusion of PGB\(_1\) by either route. Bile flow actually declined continuously throughout both infusion periods. It declined from a control value of 1.27 ± 0.20 (S.E.) to 1.14 ± 0.25 (S.E.) ml/hr/100 grams by the end of the portal venous infusion, and dropped from a control level of 1.10 ± 0.26 (S.E.) to 1.01 ± 0.20 (S.E.) ml/hr/100 grams by the end of the hepatic arterial infusion. There was a total 21 per cent decrease in bile flow by the end of the second infusion period. Hepatic arterial flow increased during both infusion periods. During the portal venous infusion period, hepatic arterial flow rose from a control value of 19.8 ± 1.8 (S.E.) to 21.0 ± 2.0 (S.E.) ml/min/100 grams, an increase of 6 per cent after 15 minutes of infusion. During the hepatic arterial infusion period, flow also increased 6 per cent by the end of the infusion period. It rose from a control value of 20.7 ± 1.9 (S.E.) to 22.0 ± 2.1 (S.E.) ml/min/100 grams. Hepatic arterial resistance decreased significantly (p < 0.01) during both infusion periods. By the end of the portal venous infusion, hepatic arterial resistance had declined from a control value of 6.13 ± 0.69 (S.E.) to 5.56 ± 0.62 (S.E.) mm Hg/ml/min/100 grams, a 9 per cent decrease. PGB\(_1\) infusion into the hepatic artery resulted in an 11 per cent decrease in resistance from a control value of 5.64 ± 0.63 (S.E.) to 5.00 ± 0.49 (S.E.). There was little or no effect on portal venous flow or intrahepatic portal venous resistance during either infusion period. Systemic arterial pressure decreased continuously by a slight amount throughout both infusion periods. It dropped from a mean control value of 130 ± 6 (S.E.) to
Figure 39. Effects of portal venous infusion of prostaglandin E₁ (80 μg/kg/hr) on liver blood flow, resistance, bile flow and systemic arterial pressure.
Figure 40. Effects of hepatic arterial infusion of prostaglandin $E_1$ (80 µg/kg/hr) on liver blood flow, resistance, bile flow and systemic arterial pressure.
127 ± 6 (S.E.) mm Hg by the end of the portal venous infusion period and declined from a control value of 127 ± 5 (S.E.) to 124 ± 5 (S.E.) mm Hg by the end of the hepatic arterial infusion period. The total decline in pressure was approximately 5 per cent. Figure 41 shows that total liver blood flow remained fairly constant during the portal venous infusion period, while bile flow decreased. Figure 42 shows that there was a slight decline in total liver blood flow during the hepatic arterial infusion of PGB₁ while bile flow also continued to decrease.

PGB₁ was infused directly into the artery serving the small intestine segment in 11 experiments at the rate of 80 μg/kg/hr for 30 minutes. The effects of this infusion are shown in Figure 43. There was a brief, transient, but significant (p < 0.01) 17 per cent increase in blood flow after 1 minute of infusion. Flow rose from a control value of 15.5 ± 1.6 (S.E.) to 18.2 ± 1.9 (S.E.) ml/min/100 grams. After 2 minutes of infusion, flow had returned to the control level, and thereafter continued to decrease until by the end of the infusion period, it had declined significantly (p < 0.01) to a value of 9.1 ± 1.1 (S.E.) ml/min/100 grams, a 41 per cent decrease. Vascular resistance dropped transiently, reflecting the brief vasodilator response seen after the onset of PGB₁ infusion. It declined from a control value of 6.96 ± 0.92 (S.E.) to 6.00 ± 1.01 (S.E.) mm Hg/ml/min/100 grams after 1 minute of infusion, a significant (p < 0.01) decrease of nearly 14 per cent. Thereafter resistance continuously increased until by the end of the infusion period, it had reached a value of 10.95 ± 1.89 (S.E.), a significant (p < 0.01) increase of 57 per cent over the control level.
Figure 41. Effects of portal venous infusion of prostaglandin B1 on total liver blood flow and bile flow.
Figure 42. Effects of hepatic arterial infusion of prostaglandin B\textsubscript{1} on total liver blood flow and bile flow.
Figure 43. Effects of intra-arterial infusion of prostaglandin B₁ (80 µg/kg/hr) on small intestine blood flow and resistance.
Systemic arterial pressure decreased continuously throughout the experiment. After 10 minutes of infusion, pressure had significantly (p < 0.01) decreased by nearly 7 per cent. By the end of the infusion period, it had declined over 15 per cent, from a control value of 130 ± 5 (S.E.) to 110 ± 7 (S.E.) mm Hg.
DISCUSSION

THE POSTPRANDIAL HEMODYNAMIC RESPONSE

It is well documented that in animals and man there is a marked postprandial increase in mesenteric blood flow (10, 17, 37, 41, 58, 99, 131, 132). Increases in mesenteric blood flow in the conscious dog range from 33 per cent to 132 per cent above control levels. The peak increase usually occurred from 30 to 90 minutes postprandially (17, 41, 58, 131, 132). Ingestion of protein in man causes a 35 per cent increase in splanchnic blood flow after one hour (10). Intraduodenal instillation of corn oil, L-phenylalanine or acid causes an increase in mesenteric blood flow of 10 to 59 per cent after a short latency ranging from 1 to 20 minutes (37).

There is disagreement as to whether the increased mesenteric blood flow is due to an increase in cardiac output, a redistribution of flow from somatic tissues or a direct vasodilation of the mesenteric vasculature. In the rat the postprandial increase in mesenteric blood flow was attributed to the increased cardiac output and not to a diversion of blood flow from other vascular beds, since there was a general increase in blood flow to all vascular beds during digestion (99). Fronek (1968) attributes increased mesenteric blood flow to a redistribution of blood flow from the somatic tissues (41). Others have found
neither a postprandial increase in cardiac output or an increase in peripheral resistance and attribute the blood flow increase to a selective mesenteric vasodilation (17, 37, 131).

The cause of the postprandial mesenteric vasodilation is not known, but there have been many speculations as to its cause (131). Since there is increased neural activity during digestion, autonomic reflexes have been implicated in controlling mesenteric blood flow. Also during digestion gastrointestinal hormones, bile acids, absorbed food stuffs, as well as other circulating humoral agents enter the splanchnic circulation and may cause vasodilation. Mechanical effects such as contact of chyme with the mucosa, increased intestinal motility and distention have also been hypothesized as possible causes of increased mesenteric blood flow.

It has been reported in both cats and dogs that postprandial mesenteric vasodilation was not prevented by alpha or beta receptor blockade or bilateral vagotomy (37, 132). In dogs mesenteric vasodilation was prevented by cholinergic blockade; however, since vagal stimulation does not increase mesenteric blood flow, neural control must be at the local level (132).

The gastrointestinal hormones secretin, pancreozymin and gastrin have been implicated in causing the postprandial vasodilation in the dog (17) and cat (37, 38, 101). Glucagon has been found to increase mesenteric blood flow in the cat (39) and dog (82) and to increase hepatic blood flow in the monkey (9). Pancreozymin and secretin have been said to cause mesenteric vasodilation indirectly through
release of bradykinin from the pancreas (60), the release of 5-hydroxytryptamine from the intestine (6), or stimulating oxygen consumption and thus causing the release of vasodilator metabolites (37). The autonomic nervous system does not seem to be involved in the vasodilator response of pancreozymin and secretin (6).

A bile salt derivative, sodium dehydrocholate, has been found to increase total liver blood flow in man (87) and to increase hepatic arterial flow in the dog (47, 87). Infusions of amino acids in man causes an increase in splanchnic oxygen consumption and blood flow (13). In dogs bathing the jejunal mucosa with hypertonic glucose solution causes a local increase in mesenteric blood flow (18, 130) which may be mediated by local neural reflexes (18).

Other humoral agents have been implicated in regulating mesenteric blood flow. The gastrointestinal tract contains high concentrations of histamine and serotonin which when infused intra-arterially dilate the intestinal vessels in the cat and dog (100, 122). Prostaglandins are also present in the small intestine and are released during digestion (133). In dogs prostaglandins $E_1$, $E_2$, $A_1$ and $A_2$ have been shown to increase blood flow in the superior mesenteric artery (97, 112). Cyclic AMP has also been implicated in mesenteric vasodilation, since its release is stimulated by prostaglandin $E_1$ in the dog, and it also causes vasodilation of the mesenteric arteries (113).

Mechanical stimulation has also been postulated to cause increased mesenteric blood flow. In the cat mechanical stimulation of the jejunal mucosa (as if from the presence of chyme) produced a
marked transient increase in total intestinal blood flow attributed to an intramural nervous reflex dependent on the release of 5-hydroxytryptamine (7). In dogs it was found that increased intestinal motility induced by metacholine had no effect on mesenteric blood flow (137). Distention of the dog small intestine decreased blood flow. Blood flow recovered somewhat, however, due to stress relaxation of the intestinal wall and autoregulatory mechanisms (50).

The effects of synthetic gastrin pentapeptide, secretin, pancreozymin, sodium dehydrocholate, sodium taurocholate, prostaglandin A₁ and prostaglandin B₁ on the hepatic arterial, intrahepatic portal venous and small intestinal vasculature, on splanchnic blood flow and on liver bile flow are discussed below. Dosages were chosen in the range of those which have been previously reported to cause some vascular or secretory response. Cardiovascular effects of these agents in our dog liver and small intestine preparations were either absent or of a rather small magnitude. It could be concluded that the postprandial hyperemia in this species as described above might involve the gastrointestinal hormones and prostaglandins to only a minor extent and the enterohepatic circulation of conjugated bile salts not at all.
PENTAGASTRIN EFFECTS ON THE SPLANCHNIC VASCULATURE

The dosages of pentagastrin used in the liver (10 µg/kg/hr) and the small intestine (5 µg/kg/hr) experiments were based on work done by Kaminski, et al (70). They infused pentagastrin intravenously in conscious dogs at dosages ranging from 1 to 12 µg/kg/hr. Mean gastric acid output increased significantly during the infusion of 1 µg/kg/hour. Maximal acid output was observed at the 8 µg/kg/hr dose (70). The dosages of pentagastrin used in our experiments are within the range of those producing significant gastric acid output and might be expected to also result in other physiological effects.

Pentagastrin has been previously shown to increase blood flow to the pancreas of the dog and the small intestine of the cat; however, there have been no studies done with pentagastrin and hepatic blood flow. Infused intravenously at the rate of 0.2 µg/kg/min (12 µg/kg/hr) in the anesthetized dog, pentagastrin caused a mean increase in pancreatic blood flow of over 2 times the control value (44). In anesthetized cats close intra-arterial infusion of 3 µg/kg/min (180 µg/kg/hr) of pentagastrin evoked an immediate and significant transient decrease in small intestinal vascular resistance and a transient peak blood flow increase of 50 per cent which vanished with continued infusion due to an increase in intestinal motility. Administration of atropine blocked the effect of pentagastrin on intestinal motility allowing a more pronounced, sustained blood flow increase that peaked at 150 per cent above the control level (38).
In our studies on the small intestine, intravenous infusion of pentagastrin at the rate of 5 µg/kg/hr produced no significant changes in intestinal blood flow or resistance or systemic arterial pressure (see Figure 24). At a dosage that produces a marked gastric acid secretory response in the dog (70), we found no increase in small intestine blood flow, possibly due to increased intestinal motility as was seen in the cat (38). However, those who have reported mesenteric blood flow increases in the dog pancreas and cat small intestine used pentagastrin dosages far in excess of those needed to produce a maximal gastric acid secretory response.

In the liver experiments pentagastrin infused at the rate of 10 µg/kg/hr produced an increase in total liver blood flow and a decrease in resistance (see Figures 22 and 23). There was an 8 per cent increase in hepatic arterial flow at 30 minutes and a significant 14 per cent increase in portal venous flow at 10 minutes after the start of the infusion. Both hepatic arterial (significantly) and intrahepatic portal venous resistances decreased by 15 per cent by 30 and 60 minutes after the start of the infusion, respectively. There was no change in systemic arterial pressure while total liver blood flow increased by 19 per cent by the end of the infusion period.

The 14 per cent increase in portal venous flow at this dosage level is possibly due in part to an increase in pancreatic venous outflow, which in the dog increased by two-fold at a pentagastrin dosage of 12 µg/kg/hour (44). Also the increase may possibly be due to an increase in small intestine blood flow, since at higher dosages of
pentagastrin there is elicited a transient mesenteric vasodilation in the cat (38). The increase in hepatic arterial blood flow may be due to direct vasodilation produced by pentagastrin or to the release of prostaglandins from the intestinal mucosa (133), since prostaglandin E$_1$ has been shown to be a direct vasodilator of the hepatic artery (43).

The peak 14 per cent increase in portal venous blood flow as compared to a range of postprandial mesenteric blood flow increases from 33 to 132 per cent above control levels seen in other studies in the dog, indicates that perhaps physiological levels of gastrin are only marginally involved in the postprandial increase in splanchnic blood flow.

PANCREOZYMIN EFFECTS ON THE SPLANCHNIC VASCULATURE

Pancreatic blood flow has been studied in the dog, and small intestine blood flow has been studied in the cat after pancreozymin administration; however, there have been no studies concerning the effects of pancreozymin on liver blood flow in any species. Pancreozymin (Boots) injected in doses ranging from 1 to 5 units/kg caused increases in pancreatic blood flow up to 3 times that of the control value in dogs (2, 44, 95). Injections of 100 units of pancreozymin (Calbiochem) into the femoral vein of the dog produced an immediate 95 per cent increase in pancreatic blood flow which returned to the control level by 10 minutes after the injection (40). In the cat
intravenous infusions of pancreozymin at doses ranging from 1.1 to 4.3 units/kg/hr caused increases in superior mesenteric flow ranging from 10 to 60 per cent above control levels (37). In another study on cats, a massive intra-arterial dose of pancreozymin (180 units/kg/hr) caused an immediate increase in mesenteric blood flow of 150 per cent which disappeared within 30 seconds due to sustained tonic contractions of the intestine (38).

In our liver experiments pancreozymin (Calbiochem) was infused intravenously at the rate of 2.73 units/min (8 units/kg/hr based on an average 20 kg animal weight) for 30 minutes. In previous canine studies pancreozymin was administered by injection rather than by infusion. Infusing pancreozymin is more physiological, since it is released continuously throughout digestion as long as protein and fat remain in the duodenum. Our dosage is within the range of those that gave a significant increase in mesenteric blood flow in the cat (37, 38), and should give an expected increase in pancreatic blood flow as seen in previous studies (2, 40, 44, 95).

In our experiments portal venous flow transiently increased by over 5 per cent after 10 minutes of the infusion; however, intrahepatic portal venous resistance, hepatic arterial flow and resistance did not change (see Figure 28). Systemic arterial pressure decreased significantly by 7 per cent by the end of the infusion. The transient increase in portal venous flow is due possibly to an increase in mesenteric flow (e.g., pancreas and small intestine), while the decline in blood flow thereafter is possibly due to the decrease in systemic
arterial pressure. These data show that pancreozymin at this dosage has no direct vasodilator effect on the hepatic vessels of the dog.

SECRETIN EFFECTS ON THE SPLANCHNIC VASCULATURE

Secretin has been shown to increase pancreatic blood flow in the dog and small intestine blood flow in the dog and cat. The effects of secretin on hepatic blood flow are conflicting. In the cat injections of secretin into the hepatic artery produced a decrease in hepatic arterial flow but no effect upon portal venous flow (102). Secretin administration in the human produced no effect on hepatic arterial width and an increase in portal venous width (128). Intravenous injections of secretin (Boots, Jorpes and Sigma) in dosages ranging from 60 to 95 units resulted in transient increases in pancreatic flow in the dog from 40 to 300 per cent (40, 44). In one study on dogs an intravenous dose of secretin (Boots, 1.5 units/kg) caused a prolonged 38 per cent increase in mesenteric blood flow (17), while in another study on dogs intravenous injection of Jorpes secretin (1 unit/kg) produced only a transient increase in mesenteric arterial flow (42). Also in cats intravenous secretin administration in doses ranging from 1.34 to 4.7 units/kg/hr resulted in almost immediate increases in superior mesenteric flow of 11 to 54 per cent above control levels (37).

In both small intestine and liver experiments, we infused secretin (Calbiochem) via the femoral vein for 20 minutes at a dosage
of 4 units/min (80 units total or 12 units/kg/hr based on 20 kg weight). Our dosage is comparable to those which caused increases in canine pancreatic blood flow (40, 44) and is greater than those which produced increases in small intestine blood flow in the dog and cat (37, 42).

By infusing rather than injecting secretin into the animal, we obtained a more physiological condition, since secretin is released throughout digestion as long as food remains in the stomach and duodenum.

Our studies on small intestine blood flow agree with others using the cat and dog, since we obtained a significant increase in blood flow of 11 per cent and a decrease in resistance of 14 per cent after 10 minutes of infusion (see Figure 27). The vasodilation persisted throughout the infusion period. In the liver experiments there was only a small transient increase in portal venous flow due probably to an increase in small intestine and pancreatic blood flow. There was no change in any of the other hepatic vascular parameters. Thus secretin may be marginally involved in the postprandial increase in mesenteric blood flow in the dog but has no effect on total hepatic blood flow.

BILE ACID EFFECTS ON THE SPLANCHNIC VASCULATURE

The effects of sodium dehydrocholate have been studied in the pancreatic, superior mesenteric and hepatic vascular beds of the canine and in the hepatic bed of the human. In the dog intravenous injections
of sodium dehydrocholate up to a total of 2 grams, produced a ten-fold increase in bile flow and an 80 mm Hg decline in systemic arterial pressure and eventually death (98). To prevent such precipitous declines in systemic arterial pressure and still use sufficiently adequate doses of sodium dehydrocholate to produce a significant bile flow response, we infused the bile salt intravenously at a constant rate of 30.6 mg/min for one hour (90 mg/kg/hr, a total of 1.8 grams) and obtained only a 14 mm Hg decline in systemic arterial pressure and up to a four-fold increase in bile flow. Smaller, intra-arterially injected dosages of sodium dehydrocholate (10 to 40 mg) have produced graded increases in canine pancreatic blood flow up to 55 per cent over control levels (95). An intravenous injection of 500 mg in the dog produced a mean increase in hepatic arterial blood flow of 48 per cent, a 29 per cent decrease in portal venous flow, a 22 per cent decrease in superior mesenteric arterial flow and no change in systemic arterial pressure or total liver blood flow (47). In contrast in the human, a 25 mg/kg dose of sodium dehydrocholate produced a mean 41 per cent increase in total hepatic blood flow. There was no decrease in systemic blood pressure (87).

In our studies total liver blood flow declined slightly by over 9 per cent (see Figure 31) due to a 13 per cent decrease in portal venous flow, since there was no change in hepatic arterial flow (see Figure 30). However, hepatic arterial resistance decreased significantly by 13 per cent indicating that there was a vasodilation. Since systemic arterial pressure decreased by 12 per cent, the decrease in
portal flow and the failure of hepatic arterial flow to increase despite the vasodilation were probably due to the systemic effects of sodium dehydrocholate infusion.

In the small intestine experiments using the same infusion rate of sodium dehydrocholate, we observed a slight, transient decline in blood flow of 11 per cent and an increase in resistance of 8 per cent by 10 minutes after the start of the infusion. Both returned to control levels, while systemic arterial pressure declined by 15 per cent by the end of the infusion period. The transient vasoconstriction observed is possibly due to a direct vasoconstrictor effect of sodium dehydrocholate or possibly due to increased tension in the intestinal wall, since bile acids increase intestinal motility.

Very little has been done concerning splanchnic blood flow after sodium taurocholate infusion. In one study on the dog, an intravenous 500 mg injection of taurocholate produced a slight mean decrease in hepatic arterial flow of 16.5 per cent. There was no decrease in systemic arterial pressure (47).

In our experiments we infused sodium taurocholate intravenously at the rate of 8.1 mg/min for one hour (or 24 mg/kg/hr, a total of 280 mg). This dosage was used because it gave a significant increase in bile flow as shown in a previous study (115). In the liver experiments there was little or no change in hepatic arterial flow or resistance while portal flow decreased by 12 per cent and intrahepatic portal resistance increased by 15 per cent by the end of the infusion period (see Figure 33). The 9 per cent decrease in total liver blood
flow due to the decreased portal flow was probably due to the slight
4 per cent decrease in systemic arterial pressure.

In the small intestine experiments there was a slight decrease
in flow and increase in resistance throughout the infusion of tauro-
cholate (see Figure 35). The slight vasoconstriction may have been due
to a direct vascular effect or to an increase in intestinal wall
tension.

From these results we conclude that neither oxidized non-
conjugated nor unoxidized conjugated bile acids are involved in the
postprandial increase in canine mesenteric blood flow. Sodium dehydro-
cholate, a synthetic, oxidized, non-conjugated bile salt, has been
shown to cause a significant increase in total liver blood flow in the
human (87); however, we have found this not to be the case in the dog.
Oxidized, non-conjugated bile acids are formed by bacterial action in
the intestine, and since they are poorly reabsorbed, would not be
found in the enterohepatic circulation during digestion. The natural
bile acid taurocholate, an unoxidized, conjugated bile acid, even
though present in the enterohepatic circulation during digestion, is
not involved in the postprandial increase in mesenteric blood flow,
since it even slightly decreases splanchnic blood flow in the dog.
PROSTAGLANDIN EFFECTS ON THE SPLANCHNIC VASCULATURE

The prostaglandins $E_1$, $E_2$, $A_1$ and $A_2$ have been shown to be vasodilators in the dog and to decrease systemic arterial pressure. Injected intra-arterially in the anesthetized dog, these prostaglandins have been shown to increase blood flow in the superior mesenteric artery (97). A 0.05 μg/kg/min intra-arterial infusion of PGE$_1$ caused an immediate 96 per cent increase in superior mesenteric artery flow which decreased to 78 per cent, 7 minutes after the start of the infusion. The decline in blood flow was attributed to the fall in systemic arterial pressure (112). Prostaglandin $E_1$ (PGE$_1$) infused via the femoral vein and also the hepatic artery caused an increase in hepatic arterial blood flow in the dog. The blood flow increase was not abolished by denervation or beta-adrenergic receptor blockade and was attributed to a direct vascular effect of PGE$_1$. The increase in portal venous flow observed was due to mesenteric vasodilation (143). There have been no reports concerning the vascular effects of the prostaglandins $A_1$ or $B_1$ on the liver.

In our liver experiments prostaglandin $A_1$ (PGA$_1$) was infused via the femoral vein at the rate of 2 μg/kg/hr for 30 minutes. In the small intestine experiments both 1 μg/kg/hr and 2 μg/kg/hr dosages were infused intra-arterially to determine the dose response of PGA$_1$ in this vascular bed. In one series of small intestine studies, a beta-adrenergic receptor blocking agent, Sotalol, was administered intravenously to determine if the mesenteric vasodilation was due to beta-
adrenergic stimulation. The PGA₁ dosages used were based on studies in the dog in which systemic arterial pressure decreased significantly after injections ranging from 0.01 to 5 µg/kilogram (3, 59).

By the end of the infusion of PGA₁, total liver blood flow decreased by 28 per cent (see Figure 37). Both hepatic arterial and portal venous flows decreased throughout the infusion period (see Figure 36). Intrahepatic portal venous resistance increased and hepatic arterial resistance remained essentially the same as the control except for a transient 6 per cent decrease, 5 minutes after the infusion was started, indicating a transient vasodilation of the hepatic artery. Systemic arterial pressure decreased continuously until by the end of the infusion of PGA₁ it had dropped by 20 mm mercury. The overall decreases in hepatic arterial and portal venous flow were for the most part probably due to the decline in systemic arterial pressure. There was only a slight transient vasodilation of the hepatic artery possibly due to a direct effect of PGA₁ on the vascular smooth muscle.

In the first series of small intestine experiments, close intra-arterial infusion of PGA₁ at the rate of 2 µg/kg/hr for 30 minutes produced a significant transient increase in blood flow of 57 per cent, one minute after the start of the infusion (see Figure 38). After 20 minutes of infusion, it had declined to a level significantly below the control. Resistance decreased transiently by 38 per cent, one minute after the start of the infusion; however, it had returned to above control levels by the end of the infusion period. Systemic
arterial pressure decreased by 17 mm Hg by the end of the infusion period.

In a second series of small intestine experiments, the dose response to PGA₁ was tested by first infusing a 1 µg/kg/hr dose and then a 2 µg/kg/hr dose for 20 minutes each (see Tables 2 and 3). The transient increase in blood flow was seen with each dosage; however, the relative increase in blood flow at the 2 µg/kg/hr dose was 43 percent greater than that at the 1 µg/kg/hr dose. The subsequent decrease in flow occurred to a relatively greater extent during the 1 µg/kg/hr infusion than during the 2 µg/kg/hr infusion. Resistance changes in both instances reflected vasodilation; the relative drop in resistance was significantly greater at the 2 µg/kg/hr dose than that at the 1 µg/kg/hr dose. During these PGA₁ infusions, there was only a slight decline in systemic arterial pressure. To test the possibility that the transient vasodilation might be due to beta-adrenergic receptor stimulation, Sotalol, a beta blocking agent, was infused intravenously at a total dosage of approximately 20 mg/kilogram. Afterwards, 2 µg/kg/hr of PGA₁ was again infused intra-arterially and the transient vasodilation was even greater than that seen before beta-adrenergic blockade. It has been shown in other studies on the dog that beta blockade produced by propranolol abolished neither the systemic vasodilator effects of PGA₁ (59) or PGE₁ (97), nor the hepatic arterial vasodilation produced by PGE₁ (43). Hepatic arterial dilator response to prostaglandin appeared to be actually enhanced, as was the small intestine vascular response in our study, after beta-adrenergic
blockade (43). The vasodilation seen in our denervated gut preparations appears to be due to a direct vascular effect of PGA₁. The transient nature of this response might be due to a tachyphylactic effect; however, repeated infusions of PGA₁ produced characteristic vasodilator responses of the same magnitude. The vasodilator response was transient even with those infusions during which systemic arterial pressure did not decrease; thus it cannot be fully explained as resulting from hypotension.

Very little has been done with the B group prostaglandins (PGB₁ and PGB₂) in the splanchnic circulation of the dog. In vitro, PGB₂ is a potent constrictor of cutaneous, mesenteric arterial and mesenteric venous vascular smooth muscle from the dog and of pancreatic arterial muscle from the rat. In dogs, PGB₁ and PGB₂ injections ranging from 4.5 to 45 µg/kg caused dose dependent decreases in systemic arterial pressure. The PGB₁ dose used in our experiments (80 µg/kg/hr) was chosen in order to produce a significant systemic effect.

In the liver experiments PGB₁ was infused directly into the liver, first via the portal vein for 15 minutes and then via the hepatic artery for 15 minutes. During the portal venous infusion period, hepatic arterial flow rose by 6 per cent and resistance decreased by 9 per cent by the end of the infusion period. There was no change in portal venous flow or intrahepatic portal venous resistance (see Figure 39 for results). During the hepatic arterial infusion of PGB₁, hepatic arterial flow increased by 6 per cent and resistance decreased
by 11 per cent while there was little or no change in portal venous flow or intrahepatic portal venous resistance by the end of the infusion period. During both infusion periods, systemic arterial pressure declined by only 3 mm Hg (for a total drop of 6 mm Hg). PGB₁ did not cause a significant decrease in systemic arterial pressure in this set of experiments due to its destruction in the liver and lungs before it reached the systemic circulation. PGB₁ may be a direct vasodilator of the hepatic artery or it may produce this effect by triggering some unknown vasodilator mechanism.

Administered intra-arterially in the small intestine experiments, a 30-minute infusion of PGB₁ (80 μg/kg/hr) produced a significant decline in systemic arterial pressure of 20 mm Hg, since the prostaglandin reached the systemic circulation before it circulated through the liver (see Figure 43). There was also a transient 17 per cent increase in blood flow that returned to the control level by 2 minutes after the start of the infusion. Thereafter it continued to decline until by the end of the infusion period it was 41 per cent below the control level. Vascular resistance transiently decreased by 14 per cent after one minute of infusion and thereafter started to increase until by the end of the infusion period it was 57 per cent above the control level. Close intra-arterial infusion of PGB₁ thus causes a transient vasodilation in the small intestine followed by a prolonged vasoconstriction. The cause of this bi-phasic response to PGB₁ infusion is unknown.
The prostaglandins \( A_1 \) and \( B_1 \) may be marginally involved in the postprandial mesenteric vasodilator response seen in the dog since gastrin causes the release of prostaglandins from the intestinal mucosa (133). Both PGA\(_1\) and PGB\(_1\) produced transient increases in mesenteric blood flow. PGA\(_1\) produced a slight, transient increase in hepatic arterial flow while the increase in flow seen after PGB\(_1\) infusion, though slight, was more prolonged.

THE CHOLERETIC RESPONSE AND ITS RELATIONSHIP TO HEPATIC HEMODYNAMICS

The secretion of bile by the liver is under the control of autonomic innervation, hormones and other chemical substances. Increased biliary flow is of two general types. A hydrocholeretic response is described as one in which there is a profuse flow of thin, watery bile with a decreased concentration of bile salts and other organic constituents, while a true choleretic response results in a modest volume increase, and the bile salt concentration may also actually be increased. The hormonal agents gastrin and certain of its structural analogues (66, 76, 88, 136), as well as cholecystokinin-pancreozymin (66), secretin (65, 96), glucagon (65) and histamine (75, 136) are among those which have been reported to increase bile flow. Many other endogenous as well as exogenously administered organic substances are cleared from the blood by the liver and result in elevated hepatic biliary flow. Thus the bile salts themselves may act as choleretics
Stimulation of the vagus increases bile flow, and the response is blocked by anticholinergic agents. Part of the response results indirectly through the vagal release of gastrin. Norepinephrine depresses while isoprenaline, a beta-adrenergic agent, stimulates bile flow in the anesthetized dog (72). Biliary responses to sympathetic neural stimulation have generally been attributed to vascular effects. However, the relationship between blood pressure and blood flow, and bile flow is not entirely clear.

Tanturi and Ivy (118) found that in dogs, a 50 per cent occlusion of the portal vein decreased bile flow, while clamping of the hepatic artery resulted in a 25 to 200 per cent increase. The former was very likely the result of general cardiovascular collapse which follows visceral pooling, although they attributed it to primary loss of portal flow. The latter effect was explained as a result of decreased intrahepatic pressure favoring opening of bile canaliculi. Section of the hepatic nerves increased bile flow while their stimulation decreased it. Nerve section after arterial occlusion did not further increase bile flow. Again they concluded that increased liver blood flow may augment bile flow except when associated with an increased intrahepatic vascular pressure.

Bile production has been studied by Brauer and coworkers (11, 12, 14, 15, 16) using isolated rat livers perfused with oxygenated blood by way of the portal vein. They found bile flow to be reduced when hepatic venous pressure was elevated (14). This has also been the
finding, by others, in anesthetized dogs (96, 118), although Donovan, et al. (31) report an increased bile flow after partial obstruction of the suprahepatic inferior vena cava. Most evidence supports the concept that bile flow is not ultrafiltration but rather an active process which is largely independent of blood pressure. In the isolated perfused rat liver preparation bile flow has been shown to have a high temperature coefficient, a $Q_{10}$ of 3.0-5.0, and rises from zero at $25^\circ C$ to a maximum at about $40^\circ C$ (15). It was also found that biliary pressure was little influenced by portal perfusion pressure, about 12 mm Hg at a portal pressure of 10 mm Hg and still about 9.5 mm Hg when perfusion pressure was reduced to 2.5 mm mercury. Bile flow in the perfused rat liver was found to be directly related to portal inflow in an almost linear fashion (11). When blood flow was reduced from 6 ml/min/gram down to 3 ml/min/gram there was a 40 per cent reduction in bile flow. The limiting factor appeared to be the quantity of oxygen delivered rather than the rate of blood flow per se. During perfusion with hyperbaric blood ($P_{O_2}$ 3000 mm Hg) bile flow remained constant until portal inflow was reduced to less than 1 ml/min/gram of liver.

Most workers have found optimum hemodynamic parameters for bile flow and other functions in isolated perfused liver preparations of larger mammalian species. Cuello-Mainardi, et al. (21) found that in the isolated pig liver perfused via the portal vein with homologous blood, bile flow was only 0.48 ml/hr at a portal flow of 0.25 ml/g/min, rose to an optimum of 2.25 at a perfusion rate of 1 ml/g/min and then
decreased to 1.45 ml/hr as portal flow was further increased to 1.5 ml/g/minute. In a similar preparation Tait, van Wyk and Eiseman (117) report optimum bile flows of about 5 ml/hr during portal vein perfusions at 0.5 to 1.0 ml/g/min which were decreased to 0.6 ml/hr at portal flows of 0.2 ml/g/minute. They also pointed out the advantage of simultaneous hepatic arterial perfusion. When perfusion flow was divided between the two inputs, bile flows were 11.5 and 4.3 ml/hr for liver blood flows of 0.5 and 0.2 ml/min/gram, respectively.

Preisig, et al. (96) studied the effect of hemorrhagic hypotension on liver blood and bile flow in anesthetized dogs. Reduction of mean arterial pressure to 41 to 71 per cent of control resulted in decreases in effective hepatic blood flow (BSP or colloid clearance) to values 30 to 80 per cent of control. Bile flow and composition were not significantly related to these changes, and under these conditions secretin and taurocholate still elicited their typical choleretic responses. This would agree with findings in the present study; hemodynamic parameters and bile flow may vary independently, at least over a certain range, and even in oppositely expected directions.

Intravenous infusion of sodium dehydrocholate at a rate of 30.6 mg/min for 60 minutes resulted in a mean increase in bile flow of nearly 4 times that seen during the control period, while liver blood flow and systemic arterial pressure slightly decreased (see Figures 30 and 31). Regan and Horrall (98) found also in anesthetized dogs that bile flow increased an average of 10 times basal rate for 2-1/2 hours following a single 2 gram intravenous dose of sodium dehydrocholate.
Grodins, et al. (47) found a qualitatively similar response to a 0.5 gram dose. In their study it was accompanied by an average 48 per cent increase in hepatic artery flow while portal flow decreased or showed no change. Liver blood flow showed a mean increase of 41.3 per cent in a group of human subjects studied by Mitchell and Torrance (87) following a single 25 mg/kg intravenous dose of sodium dehydrochololate, while bile flow rose to a peak 95 to 300 per cent of control rate after 20 to 25 minutes and returned to normal after 2 hours.

Sodium taurochololate in the present study was infused intravenously at a rate of 8.1 mg/min for 60 minutes. The mean increase in bile flow was over two-fold while again liver blood flow (portal only) and systemic arterial pressure were slightly decreased (see Figures 33 and 34). Soloway, et al. (115) infused taurochololate at the same rate for a period of three hours and maintained bile flow at about 1.7 times control level. Hepatic arterial flow was generally decreased (mean 16.5 per cent decrease) by a single 0.5 gram dose of taurochololate in the experiments of Grodins, et al. (47).

It has been found that the oxidized unconjugated products such as dehydrochololate produce a hydrocholeretic response, while the unoxidized conjugated bile acids such as taurochololate result in a true choleresis when exogenously administered (5). The results of Grodins, et al. (47) led them to conclude that a hydrocholeresis such as that produced by sodium dehydrochololate, mixed triketocholanates or cinchopin is accompanied by increased hepatic artery flow, while the choleric response to sodium taurochololate and sodium glycochololate is not. Typical
hydrocholeresis and true choleresis have been produced by dehydro-
cholate and conjugated bile salts, respectively, in the isolated rat
liver perfused with arterial blood by way of the portal vein. Thus
Brauer and Pessotti (16) concluded that if sufficient oxygen is
supplied to the liver either type of choleretic response may occur
without a change in blood flow, and that the response of the vascu-
ture is an indirect action resulting from differences in the direct
effects of various substances on metabolism of the hepatic paren-
chyma.

The intravenous infusion of secretin at a rate of 4 units/min
for 20 minutes resulted in a bile flow increase to a rate over 2.6
times that seen during the control period, while there was only a
slight increase (ca. 5 per cent) in liver blood flow and no change in
systemic arterial pressure (see Figures 25 and 26). In dog experiments,
which were similar except for the addition of a background taurocholate
infusion to maintain a constant baseline bile flow, Jones, et al. (65)
infused secretin at dose rates from 0.25 to 4.0 units/kg/hr for 2 hours.
Bile flow increased from a control value of 2.4 to 5.2 ml/15 min, an
increase of about 2.2 times control, when secretin was given at the
highest dose rate. This infusion rate was about one-third that used
in the present study. They found that bicarbonate and chloride con-
centration increased while bile salt concentration decreased. Another
group (115) infused 2 units/kg/hr and increased bile flow about 2.4
times control.
Pancreozymin (cholecystokinin) was infused at a rate of 2.73 units/min for 30 minutes and resulted in an increase in bile flow of more than 1.7 times that seen during the control period. Liver blood flow (portal only) was only slightly (ca. 5 per cent) increased, while systemic arterial pressure was slightly decreased (see Figures 28 and 29). Jones and Grossman (66) infused porcine cholecystokinin intravenously in dogs at dose rates of 1 to 8 units/kg/hr for 2 hours. It was a more potent choleretic than either gastrin II or caerulein. Bicarbonate concentration was increased and also chloride concentration to a lesser extent. Their highest dose rate was comparable to that used in the present study and increased bile flow to about twice its control value.

Pentagastrin in the present study was intravenously infused at a rate of 10 μg/kg/hr for one hour. There was only a slight choleretic response; a transient 17 per cent increase. Liver blood flow (both arterial and portal) increased, amounting to about a 16 per cent increase in total flow (see Figures 22 and 23). Kaminski, et al. (70) administered pentagastrin to conscious dogs in doses of 1 to 12 μg/kg/hr for 2 hours. There was no change in bile flow or composition even at the highest dose rate used while gastric acid output increased over nine-fold. In a similar preparation using the feline, Konturek, et al. (76) found it necessary to give massive doses (40 to 80 μg/kg) of pentagastrin as a single injection in order to achieve a significant choleretic response. After one hour there was an increase in bile flow of about 50 per cent, while gastric acid output was maximal rising to
2000 μEq/hour. Natural gastrin II when given to dogs at a rate of 2 μg/kg/hr for 2 hours also resulted in a bile flow increase of about 50 per cent, a rise in gastric acid output to over 50 mEq/hr, an increase in bile bicarbonate concentration and no change in chloride concentration (66). In another study a similar choleretic response was seen by Zaterka and Grossman (136) using a dose of 4 μg/kg/hr for 90 minutes. There have been other studies in which gastrin (126) or pentagastrin (75) have been reported to not increase bile flow, again possibly because of inadequate dosage. It appears unlikely that postprandial gastrin levels would be high enough to directly promote a very significant portion of the choleretic response to the ingestion of a meal. In one study using dogs with an antral pouch and gastric fistula, the stimulated release of endogenous gastrin resulted in a bile flow increase of about 25 per cent (88). When a similar experiment was done by another group, they concluded that the biliary response was for the most part an indirect one resulting from secretin released as acid leaked into the small intestine (104).

Neither the femoral venous infusion of prostaglandin A₁ at a rate of 2 μg/kg/hr for 30 minutes nor the hepatic arterial or portal venous infusion of prostaglandin B₁ at a rate of 80 μg/kg/hr for 15 minutes produced any choleretic effect in the present study. Bile flow declined throughout the infusion period about 16 per cent during 30 minutes of PGA₁ and 21 per cent during the 45 minute PGB₁ protocol. During prostaglandin A₁ infusion there was a 12 per cent decrease in hepatic arterial flow while portal venous flow and systemic arterial
pressure were also decreased by a significant 16 per cent. There was a slight increase (ca. 5 per cent) in hepatic artery flow and a 5 per cent decrease in systemic arterial pressure during prostaglandin $E_1$ infusion (see Figures 36, 39 and 40). This biliary response is typical of the expected decline in bile flow which occurs after interruption of the enterohepatic circulation. In order to collect bile samples, the enterohepatic circulation was interrupted in the present study. Samples were collected, usually for a 10 minute period, and flow expressed as the mean during that interval. Infusions were begun after a 60 minute control period. The effects of this procedure are shown by the data in Figure 44 taken from 8 dog experiments in which the common bile duct was cannulated and drained to the exterior (Hanson, K.M. and J.A. Post, unpublished data). Four successive 30 minute bile samples were collected, analyzed for bile acid content and mean flow rate calculated. The decline in bile flow due to depletion of the bile acid pool is evident; 43.6 mEq/L in the first 30 minute sample decreasing to 29.2 mEq/L in the fourth 30 minute sample. During the same 90 minute period bile flow fell from 1.4 down to 0.9 ml/hr/100 grams of liver. In the present study infusions were begun at the point designated as 30 minutes in Figure 44. During the next succeeding 30 minute period bile flow declined by over 15 per cent. This would account for the response seen during the prostaglandin infusion. If corrected there would actually be no net change in bile flow. This correction would not contribute significantly to any of the other biliary responses except in the case of the modest effect seen during
Figure 44. Effects of continuous exterior drainage of bile on bile flow, bile acid concentration and bile acid output.
pentagastrin infusion.

It would appear from our results that bile flow increases of several fold may occur, be they hydrocholeretic (dehydrocholate and secretin) or not, with little or no change in liver blood flow. Even the small changes when seen usually involved only the portal flow; only the slight increase with pentagastrin and the decreases with taurocholate and prostaglandin A₁ were statistically significant. No agent caused a statistically significant change in hepatic arterial flow.
SUMMARY

1. The effects of the gastrointestinal hormones secretin, pancreaticin and synthetic gastrin pentapeptide, the bile salts, sodium taurocholate and sodium dehydrocholate, and the prostaglandins $A_1$ and $B_1$ on canine liver and small intestine hemodynamics were studied in over 130 experiments. These compounds were evaluated as to their possible involvement in the postprandial increase in mesenteric blood flow in the dog. An isolated in-situ liver preparation and a small intestine segment served by a single artery and vein were used in this study. Blood flows were measured with electromagnetic blood flowmeters.

2. Pentagastrin, infused intravenously, produced no significant changes in intestinal blood flow, vascular resistance or systemic arterial pressure. It produced a small increase in total liver blood flow (both hepatic arterial and portal venous) and a decrease in hepatic resistances. This study indicates that physiological levels of gastrin are possibly marginally involved in the postprandial mesenteric vasodilation.

3. In the liver experiments intravenous infusion of pancreaticin produced only a transient increase in portal venous flow with little change in other hepatic vascular parameters. This slight blood flow increase was very likely due indirectly to an increase in mesen-
teric blood flow since pancreozymin itself had no direct vasodilator effect on the hepatic vasculature.

4. Intravenous infusions of secretin produced a significant increase in small intestine blood flow and a slight transient increase in portal venous flow (again due to the increased mesenteric flow) but no change in any other hepatic vascular parameter. Secretin and pancreozymin may both be somewhat involved in postprandial mesenteric vasodilation as seen in the dog.

5. Infusions via the femoral vein of the bile salts, sodium dehydrocholate and sodium taurocholate, caused a decrease in total liver blood flow which apparently was due to decreased systemic arterial pressure. Infusions of either bile salt produced vasoconstriction in the small intestine. Since the bile salts, on the basis of our findings, appear to decrease splanchnic blood flow, their enterohepatic circulation is very likely not involved in the postprandial increase in mesenteric blood flow.

6. Close intra-arterial infusion of prostaglandin A₁ (2 μg/kg/hr) in the small intestine resulted in a transient increase in blood flow that was not abolished by Sotalol, a beta-adrenergic blocking agent. Femoral vein infusion of prostaglandin A₁ produced a significant decrease in total liver blood flow apparently caused by the decline in systemic arterial pressure, although the hepatic arterial vasculature may have actually been dilated, at least initially. During both the direct hepatic arterial and portal venous infusions of prostaglandin B₁ (80 μg/kg/hr), hepatic arterial blood flow increased while portal
venous flow did not change. Close intra-arterial infusion of prostaglandin $B_1$ produced a transient increase in small intestine blood flow followed by a sustained vasoconstriction. The cause of this bi-phasic response is unknown. Thus the prostaglandins $A_1$ and $B_1$ if released into the circulation might be involved to some extent in the canine postprandial increase in mesenteric blood flow.

7. Intravenous infusions of the bile salts, sodium dehydrocholate and sodium taurocholate, produced significant increases in bile flow as did the hormones, secretin and pancreozymin. Intravenous pentagastrin infusion produced only a slight choleric response while neither prostaglandin ($A_1$ or $B_1$) infusion resulted in any choleric effect. It would appear that bile flow increases of several fold may occur with little or no change in liver blood flow or even in the face of a significant decrease in blood flow.

8. There are indications that the gastrointestinal hormones gastrin, pancreozymin and secretin might be marginally involved in the canine postprandial mesenteric vasodilation, while it seems the bile salts do not play a role in eliciting this response. There is evidence that during digestion, gastrin may cause prostaglandins to be released from the intestinal mucosa. However, the prostaglandins $A_1$ and $B_1$ produced only transient increases in mesenteric blood flow and thus would contribute only to a small extent in the postprandial response. Of the compounds evaluated in this study, none, when given at physiological levels, would appear to be of major significance in causing increases in splanchnic blood flow of a magnitude compatible to those reported to occur postprandially in the dog.
BIBLIOGRAPHY


