PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 170, 391–397 (1982)

MINIREVIEW

Prostaglandins and the Splanchnic Circulation (41448)

ROBERT H. GALLAVAN, JR. AND EUGENE D. JACOBSON[1]

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

In 1930, Kurzok and Lieb (1) reported that seminal plasma contracted uterine smooth muscle. Subsequently, Goldblatt (2) and von Euler (3) observed that acidic lipid extracts of seminal plasma contained a potent vasodepressor that von Euler designated as "prostaglandin." Since that time, much research has been conducted to determine the role of prostaglandins (PG) in the regulation of cellular and organ functions. The purpose of our review is to summarize more recent evidence about the role of PG in the regulation of the mesenteric circulation.

Synthesis and Release. The first determination of the structure of a prostaglandin was made by Bergstrom and Sjovall in 1957 (4). Since then the structure and biosynthetic pathways of many PG have been determined. The major PG in mammals are bisenoic and are derived from the polyunsaturated fat arachidonic acid. Arachidonic acid may be synthesized from the essential fatty acid linoleic acid or it may be obtained directly from the diet. It is present in the phospholipid component of cellular membranes in all tissues and is liberated by the action of phospholipase A_2. Since release of arachidonate is the rate-limiting step in prostaglandin synthesis, and since phospholipase activity is extremely sensitive to mechanical and chemical stimuli, even small changes in the cellular environment can result in the release of substantial amounts of PG (5).

Once released, arachidonic acid is rapidly converted to a variety of PG by means of the pathways shown in Fig. 1. The immediate products of arachidonic acid metabolism are the unstable endoperioxides (PGG_2 and PGH_2), which decompose further into the more stable prostaglandins (PGD_2, PGE_2, $PGF_{2\alpha}$), prostacyclin (PGI_2) and thromboxane A_2 (TxA_2). PGI_2 and TxA_2 are rapidly converted into 6-keto $PGF_{1\alpha}$ and TxB_2, respectively (5). The most common method of inhibiting prostaglandin synthesis is to block the conversion of arachidonic acid to PGG_2 with nonsteroidal anti-inflammatory agents such as aspirin, indomethacin, mefenamic acid, and others.

The first evidence of PG release in the gastrointestinal tract was provided by Vogt (6) in 1949 who reported that frog intestinal dialysates contained a compound which was capable of stimulating contraction of smooth muscle. This dialysate was later found to contain a mixture of PG of the E and F types (7). Subsequent studies indicate that the gastrointestinal tract is capable of synthesizing a wide range of PG.

Bennet *et al.* (8) reported the presence of arachidonic acid, 6-keto $PGF_{1\alpha}$, and TxB_2 in extracts of homogenized human stomach, ileal and colonic mucosa and muscularis. In addition, the mucosal extracts contained PGD_2, PGE_2, and $PGF_{2\alpha}$. This is somewhat different from the findings of LeDuc and Needleman in the dog (9) who reported that the major products of PG synthesis by microsomal preparations taken from the length of the canine gastrointestinal tract were PGI_2 and TxB_2, al-

[1] To whom correspondence should be addressed.

0037-9727/82/080391-07$01.00/0

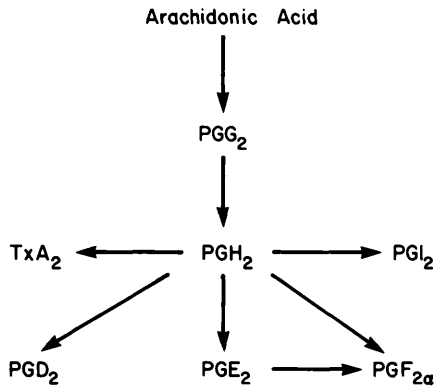

FIG. 1. Biosynthetic pathways of the major prostaglandins. PG, prostaglandin; Tx, thromboxane.

though low levels of PGE_2 and $PGF_{2\alpha}$ were also evident. High levels of PGE_2 have been reported in the human stomach and duodenum (10) and cat ileum (11) and spleen (12).

Release of PG into the mesenteric circulation has been shown to increase under a variety of conditions. Pipili and Poyser (13) noted that adrenergic stimulation of mesenteric arteries increased the rate of release of both PGI_2 and PGE_2, while KCl significantly increased $PGF_{2\alpha}$ release. Simmet and Hertting (14) studied the effects of a number of vasoconstrictors on PG release by rabbit mesenteric artery and portal vein and found that K^+, angiotensin II, and bradykinin induced the release of PGE_2 and, to a lesser extent, $PGF_{2\alpha}$. Similarly, norepinephrine and sympathetic nerve stimulation have been shown to increase PG levels in the venous effluent of the feline spleen (12, 15).

Other stimuli which enhanced gastrointestinal PG synthesis included hypertonicity (16), mechanical stimulation of the mucosa (17), and intraarterial infusions of acetylcholine (11). Once released, the PG are metabolized by 15-prostaglandin dehydrogenase and other enzymes concentrated in the tissues of the gastrointestinal tract (18), the liver (19) and the lung (19, 20).

Mechanism of Action. Work by Coceani and Wolfe (21) indicates that, in smooth muscle at least, the PG act at the level of the plasma membrane and not intracellularly. It has also been shown that the prostaglandins interact with sulfhydryl groups on or in the plasma membrane of vascular smooth muscle (22). Furthermore, the PG appear to have their own vascular smooth muscle receptors which are distinct from the α- and β-adrenergic and muscarinic cholinergic receptors of the autonomic nervous system (23).

The mechanisms by which the various PG act upon vascular smooth muscle are uncertain. Prostaglandins alter membrane electrical activity and conductance, cellular Ca^{2+} activity and cyclic nucleotide activity. However, at present no single mechanism of action appears adequate to account for the variety of effects of PG (24).

Prostaglandins and Vascular Smooth Muscle in Vitro. *Direct effects.* The effects of the various PG on vascular smooth muscle *in vitro* are inconsistent and appear to vary with the source of the muscle, the investigator, and the buffer solutions used. Hatano *et al.* (26) reported that PGE_2 (up to 3×10^{-5} *M*) and $PGF_{2\alpha}$ (up to 3×10^{-5} *M*) contracted canine mesenteric artery strips and that they were equally potent. PGI_2 and PGE_1 (both at 10^{-7} *M*) were potent relaxing agents although PGE_1 did cause contraction in some cases. At higher doses (3×10^{-6} *M*) PGI_2 caused abrupt and near maximal contractions. PGD_2 was unpredictable and sometimes elicited a biphasic response.

The work by Hatano *et al.* (26) differs from earlier work by Greenberg *et al.* (22) using canine mesenteric arteries and veins in which the authors reported that PGE_2 (5.6×10^{-6} *M*) decreased vascular smooth muscle tone while $PGF_{2\alpha}$ (6.3×10^{-7} *M*) had no effect. More recent work by Manku *et al.* (27) on rat mesenteric artery strips indicates that PGE_1 (10^{-6} *M*), PGE_2 (10^{-7} *M*), and PGI_2 (10^{-9} *M*) have no effect on vascular smooth muscle tension. Yabek and Avener (28, 29) have found that PGE_1 (1.5×10^{-6} *M*) had no effect on neonatal lamb mesenteric artery tension but that PGI_2 (10^{-6} *M*) relaxed the arterial strips slightly (14%).

Indirect effects. In addition to their direct action on vascular smooth muscle, PG also appear to potentiate or inhibit the action of a variety of drugs on vascular smooth mus-

cle. In the rat indomethacin inhibited the mesenteric arterial constrictor response to norepinephrine (30, 31), an effect reversed by PGE_2, which appears to facilitate Ca^{2+} influx (30), and by PGE_1 (32) and arachidonic acid (30, 32). In rat mesenteric artery strips the constrictor responses to angiotensin II, arginine vasopressin, K^+, Ca^{2+}, histamine, and serotonin were also inhibited by indomethacin, aspirin, and mefenamic acid and were enhanced by PGE_2 (31). At low doses (2.8×10^{-13} to 2.8×10^{-11}), PGE_1 potentiated the response of rat mesenteric arteries to norepinephrine (27, 32) and angiotensin II (27) but inhibited the response at higher doses (27). Neither PGI_2 nor PGE_2 had any effect on K^+-induced contractions in the rat, although PGI_2 inhibited the response to norepinephrine and angiotensin II (27).

The effects of PG on the response to adrenergic stimuli in other species are completely opposite to those in the rat. In rabbit mesenteric arteries, arachidonic acid and PGE_2 suppressed the response to norepinephrine while indomethacin accentuated it (32). Indomethacin also enhanced the response of neonatal lamb mesenteric arteries to electrical stimulation and norepinephrine injection while both PGI_2 and PGE_1 antagonized the response (28, 29).

In canine mesenteric arteries and veins, $PGF_{2\alpha}$ enhanced the constrictor response to epinephrine (23, 33) by a direct effect on the vascular smooth muscle (33). $PGF_{2\alpha}$ also augmented the response to serotonin and angiotensin but the mechanism of action in this case apparently involves enhancement of adrenergic neurotransmitter release by these agents, since it is blocked by reserpine (33).

Prostaglandins and the Splanchnic Circulation in Vivo. *Stomach.* Prostaglandins can alter gastric blood flow by their direct effects on vascular smooth muscle and by their indirect effects on gastric function, particularly their antisecretory effects. When applied topically or infused intraarterially or intravenously in the resting stomach, PGE_1 (34, 35), PGE_2 (36, 37), and PGI_2 (37, 38) increased blood flow. The analog 16, 16-dimethyl PGE_2 applied topically on the resting stomach increased gastric blood flow (39). When given orally, 16, 16-dimethyl PGE_2 did not affect gastric mucosal blood flow in the denervated gastric pouch (40). Most studies of the gastric circulation used the aminopyrine clearance technique (35) to measure blood flow and as such represent the effects of these prostaglandins on gastric mucosal blood flow only. In the dog, radiolabeled microsphere studies demonstrated that intraarterial PGE_1 (34) and PGI_2 (38) increased both total and mucosal blood flow.

Treatment of the stomach preparations used in these studies with indomethacin or aspirin decreased total gastric blood flow and this decrease in blood flow was confined to the gastric mucosal–submucosal layer (36, 41–43). The major site of increased resistance in this case was the submucosal arterioles which are in series with the mucosal arterioles (36). These studies indicate that PG can alter resting gastric blood flow and that they may play a role in the maintenance of resting gastric mucosal blood flow.

Additional studies indicate that PG also play a role in the regulation of gastric secretory activity and, as a result, exert an indirect effect on gastric blood flow in the stimulated stomach. Arachidonic acid, the prostaglandins E_1, E_2, and I_2 and 16,16-dimethyl PGE_2 have been shown to inhibit gastric acid secretion induced by either histamine or pentagastrin (34, 39, 41, 44–46) and both indomethacin and aspirin potentiate pentagastrin-induced secretion (47). Furthermore, PG appears in the gastric juices in a circadian rhythm which coincides with that of acid secretion (48).

Although there appears to be some species differentiation, intraarterial infusion or topical application of the PG listed above during periods of pharmacologically elevated gastric acid secretion and mucosal blood flow resulted in a decrease in both secretory activity and mucosal blood flow. In the dog, PGE_1, PGE_2, PGI_2, and 16,16-dimethyl PGE_2 decreased both blood flow and acid secretion to the same extent so that the ratio of blood flow to acid secretion remained constant (40, 43, 50). This may

indicate that the antisecretory effect of the PG is the dominant factor in the reduction of blood flow (45, 49). This is further supported by the findings of Wilson and Levine (51) that the initial response to dilator PG during acid secretion is a vasodilation which appears to shunt blood flow through the submucosal layer and that the steady state response is a reduction in both blood flow and secretion.

There has been only one study on the effects of PG on gastric blood flow and oxygen consumption. Walus *et al.* (37) reported that PGE_2 and PGI_2 increased both blood flow and oxygen consumption in the resting and histamine-stimulated stomach. However, they also reported that arachidonic acid (which should induce local release of PG) decreased both blood flow and oxygen consumption in the histamine-stimulated stomach. The effect of arachidonic acid was inhibited by indomethacin. Constant flow studies indicated that the direct effects of PGE_2 and PGI_2 were to decrease oxygen consumption and dilate the vasculature in both the resting and stimulated preparations; on the other hand arachidonic acid constricted the vessels and decreased oxygen consumption. Again, the effects of arachidonic acid were inhibited by pretreatment with indomethacin (37). From their data the authors suggested that arachidonic acid induced thromboxane synthesis.

Questions have been raised about the type of preparation employed in the previous study in which only a part of the gastric circulation was perfused while the rest was ischemic (52). It was concluded that dilator interventions or changes in perfusion pressure probably recruited additional tissue from ischemic border regions resulting in overestimations of blood flow per unit weight of tissue and oxygen consumption. Arachidonic acid is a mild vasodilator and its major action is the local release of PG, which would be inhibited in ischemic regions due to low tissue pO_2. Therefore, its action in both natural flow and constant flow preparations is a better indication of the effects of PG on gastric oxygen consumption. The finding of Walus *et al.* (37) that arachidonic acid infusion decreased gastric blood flow and oxygen consumption during histamine stimulated secretion further supports the data of other authors indicating that the metabolic effects of PG dominate their direct vascular effects in the actively secreting stomach.

Intestine. The majority of studies of PG on intestinal blood flow and function have concentrated on the small intestine. Among the major PG, it is well established that PGE_1 (53–56), PGE_2 (57–60), and PGI_2 (38, 60, 61) are intestinal vasodilators with the majority of the PGI_2-induced hyperemia directed to the mucosal layer (61). Prostaglandin $F_{2\alpha}$ has been reported to decrease canine mesenteric blood flow (53, 56, 57, 60) to dilate the human mesenteric vasculature (62), and to have variable or no effects on porcine (59) and rat intestinal circulation (63).

Although Chapnick *et al.* (60) have reported that PGD_2 decreases intestinal blood flow, both Fondacaro *et al.* (61) and Lippton *et al.* (58) have found that it elicits a biphasic response, i.e., PGD_2 infusion produced a transient vasoconstriction followed by a pronounced vasodilation. Furthermore, Fondacaro *et al.* (61) found that PGD_2 actually decreased mucosal blood flow in the steady state of the hyperemic response, redistributing blood flow to the muscularis layer.

Due to its short half-life, the effects of TxA_2 on the intestinal circulation are uncertain; however, intraarterial infusion of its metabolite TxB_2 also produced a biphasic response, namely an initial vasodilation followed by a prolonged vasoconstriction (62). Although infusions of the endoperoxide PGH_2 produced a mesenteric hyperemia (64), it is likely that it was converted to PGI_2 in the circulation, since infusion of stable endoperoxide analogs decreased mesenteric blood flow (64).

Overall, prostaglandin synthesis in the resting intestinal circulation appears to favor the vasodilator PG. Intraarterial infusions of arachidonic acid produced a vasodilation which was inhibited by pretreatment with indomethacin (60). Furthermore, cyclooxygenase inhibitors were reported to decrease superior mesenteric artery blood

flow in man (55), cats (11), and dogs (60). Studies in conscious animals using radiolabeled microspheres indicated that the cyclooxygenase inhibitors diminished both duodenal and jejunal blood flow (42, 43); however, in cats at least, they had no effect on terminal ileal or colonic blood flow (43).

As in the stomach, PG have been shown to alter intestinal cellular activity which may in turn alter intestinal blood flow. Both PGI_2 (61) and PGE_1 (56) increased intestinal oxygen consumption under free flow conditions. Prostaglandin $F_{2\alpha}$ decreased oxygen consumption at low doses (53, 56) but increased oxygen consumption at high doses (65), an effect which may be related to enhanced intestinal motor activity. Prostaglandin D_2 increased oxygen consumption at low doses (61, 65) but decreased intestinal oxygen consumption at high doses (65). The decrease in oxygen consumption with PGD_2 at high doses may be due to reductions in mucosal blood flow despite an overall increase in intestinal blood flow (65).

The action of PGE_1 on intestinal oxygen consumption may be related to its effects on intestinal secretion and absorption. Intraarterial infusion of PGE_1 produced a net secretion of water and electrolytes into the intestinal lumen (54, 66, 67) and increased transmucosal protein flux (54). The net increase in water and electrolyte secretion was attributed to both an increase in unidirectional Na^+ and water movement from blood to lumen and a decrease in Na^+ and water flux from lumen to blood (66).

Although PG may be important in the maintenance of resting intestinal blood flow, they appear to inhibit food-induced jejunal hyperemia (68). Treatment of jejunal segments with indomethacin or mefenamic acid resulted in a substantial increase in the food-induced increase in both intestinal blood flow and oxygen consumption. This would imply that prostaglandins have an antimetabolic effect when food is present in the lumen and, indeed, PGE_2 and $PGF_{2\alpha}$ have been shown to inhibit glucose absorption by several authors (57, 58, 66). Sit *et al.* (69) found that glucose-induced increases in intestinal oxygen consumption were related to both the absorption and metabolism of glucose. Preliminary results by Gallavan and Chou indicate that carbohydrate metabolism is enhanced when food is in the lumen following cyclooxygenase inhibition.

Liver, pancreas, and spleen. The vascular effects of PG on these organs are difficult to assess due to the complexity of the vascular anatomy and physiology. This is further complicated in the liver by the reciprocity of flow between the hepatic arterial and portal venous circulations. Thus, the finding by Bill (42) that rabbit hepatic arterial blood flow increased 50% following indomethacin infusion could be interpreted to mean that PG release inhibited blood flow in the resting liver. However, it could also be interpreted to mean that PG have no role in the maintenance of hepatic blood flow and that indomethacin indirectly decreased portal flow by virtue of its intestinal constrictor activity; the decline in portal flow would prompt a compensatory increase in hepatic arterial blood flow. The latter explanation may in fact be the case, since Skarstein (43) reported that indomethacin had no effect on feline hepatic blood flow.

Prostacyclin had no effect on hepatic artery blood flow (70). Intraarterial infusions of PGE_1 significantly increased hepatic artery blood flow but had no effect when infused intraportally (71). Prostaglandin $F_{2\alpha}$ is a potent portal venoconstrictor (72).

Studies of PG and the pancreatic circulation have been hampered by the fact that PG must be infused systemically in order to insure that all portions of the pancreatic circulation are affected. This is usually accompanied by development of systemic hypotension (73, 74) and a decrease in pancreatic blood flow due to sympathoadrenal discharge (73). Thus, systemic administration of PGI_2, PGE_1, and PGE_2 reduced pancreatic secretion and blood flow (73, 74) even though PGE_1 and PGE_2 dilated the isolated rat pancreas (75) and stimulated pancreatic secretion *in vitro* (73). Prostaglandin $F_{2\alpha}$ had no effect on pancreatic blood flow or secretion in the cat (73) but constricted the vasculature of the isolated rat pancreas (75) and enhanced opacifica-

tion of human pancreatic angiographs (76). Indomethacin had no effect on pancreatic blood flow in the cat (43).

The prostaglandins E_1 (77), E_2 (77), and I_2 (38) increased splenic blood flow and indomethacin blocked basal splenic prostaglandin release and increased splenic vascular resistance by 250% in the cat (12). However, indomethacin had no effect on splenic blood flow in the rabbit (42). Indomethacin enhanced the vasoconstriction induced by epinephrine, norepinephrine, angiotensin II, and neural stimulation in the cat (78).

Summary. Prostaglandins elicit a wide range of responses in the circulation of the gastrointestinal tract, liver, pancreas, and spleen. Various PG either contract or relax vascular smooth muscle and also stimulate or inhibit absorption or secretion, stimulate or inhibit cellular metabolism, potentiate or inhibit the action of various agents on splanchnic organs, and they appear to play a role in cytoprotection of the gastrointestinal mucosae. The fact that they are synthesized and released throughout the gastrointestinal tract and that inhibition of their synthesis alters the response of these organs to different physiological stimuli argues for an important physiological role for PG as regulators of gastrointestinal functions. Recent advances in assay techniques and continuing efforts to find specific prostaglandin antagonists bear promise for future elucidation of the process of release of prostaglandins in different tissues. It is not unlikely that the splanchnic microcirculation will be among the structures shown to be controlled normally by locally released prostaglandins.

1. Kurzok, R., and Lieb, C. C. Proc. Soc. Exp. Biol. Med. **28**:268–272 (1930).
2. Goldblatt, M. W. J. Physiol. (London) **84**:208–218 (1935).
3. von Euler, U. S. Klin. Wochenschr. **14**:1182–1183 (1935).
4. Bergstrom, S., and Sjovall, J. Acta Chem. Scand. **11**:1086–1087 (1957).
5. Vane, J. R., and Moncada, S. Acta Cardiol. **23**:21–37 (1979).
6. Vogt, W. Arch. Exp. Pathol. Pharmakol. **206**:1 (1949).
7. Vogt, W., Suzuki, T., and Babillis, S. Mem. Soc. Endocrinol. **14**:137 (1966).
8. Bennett, A., Hensby, C. N., Sanger, G. J., and Stamford, I. F. Brit. J. Pharmacol. **74**:435–444 (1981).
9. LeDuc, L. E., and Needleman, P. J. Pharmacol. Exp. Ther. **211**:181–188 (1979).
10. Konturek, S. J., Obtulowicz, W., Sito, E., Oleksy, J., Wilkon, S., and Kiec-Dembinska, A. Gut **22**:283–289 (1981).
11. Sanders, K. M., and Ross, G. Amer. J. Physiol. **234**:E204–E208 (1978).
12. Ferreira, S. H., and Moncada, S. Nature New Biol. **231**:237–239 (1971).
13. Pipili, E., and Poyser, N. L. Brit. J. Pharmacol. **72**:89–93 (1981).
14. Simmet, T., and Hertting, G. Eur. J. Pharmacol. **65**:325–331 (1980).
15. Ferreira, S. H., Moncada, S., and Vane, J. R. Brit. J. Pharmacol. **49**:86–97 (1973).
16. Knapp, H. R., Oelz, O., Sweetman, B. I., and Oates, J. A. Prostaglandins **15**:751–757 (1978).
17. Beubler, E., and Juan, H. Naunyn-Schmiedeberg's Arch. Pharmacol. **305**:91–95 (1978).
18. Peskar, B. M. Acta Hepatogastroenterol. **25**:49–51 (1978).
19. Ferreira, S. H., and Vane, J. R. Nature (London) **216**:868–873 (1967).
20. Hawkins, H., Smith, J., Nicolaou, K., and Eling, T. Prostaglandins **16**:871–884 (1978).
21. Coceani, F., and Wolfe, L. S. Canad. J. Physiol. Pharmacol. **44**:943–950 (1966).
22. Greenberg, S. P., Kadowitz, J., Long, J. P., and Wilson, W. R. Circ. Res. **39**:66–76 (1976).
23. Kadar, D., and Sunahara, F. A. Canad. J. Physiol. Pharmacol. **47**:871–879 (1969).
24. Bolton, T. B. Physiol. Rev. **59**:606–718 (1979).
25. Greenberg, S., Long, J. P., and Diecke, F. P. J. Arch. Int. Pharmacodyn. **204**:373–389 (1973).
26. Hatano, Y., Kohli, J. D., Goldberg, L. I., and Fried, J. Prostaglandins **21**:515–529 (1981).
27. Manku, M. S., Horrobin, D. F., Cunnane, S. C., Ally, A. J., Karmazyn, M., Karmali, R. A., Morgan, R. O., Nicolaou, K. C., and Barnette, W. E. Biochem. Biophys. Res. Comm. **83**:295–299 (1978).
28. Yabek, S. M., and Avner, B. P. Prostaglandins **17**:227–233 (1979).
29. Yabek, S. M., and Avner, B. P. Prostaglandins **19**:23–30 (1980).
30. Adeagbo, A. S. O., and Okpako, D. T. Brit. J. pharmacol. **71**:75–81 (1980).
31. Manku, M. S., and Horrobin, D. F. Prostaglandins **12**:369–375 (1976).

32. Malik, K. U., Ryan, P., and McGiff, J. C. Circ. Res. 39:163–168 (1976).
33. Greenberg, S., Kadowitz, P. J., Diecke, F. P. J., and Long, J. P. Arch. Int. Pharmacodyn. 206:5–18 (1973).
34. Cheung, L. Y., and Lowry, S. F. Surgery 83:699–704 (1978).
35. Jacobson, E. D., Linford, R. H., and Grossman, M. I. J. Clin. Invest. 45:1–13 (1966).
36. Guth, P. H., and Moler, T. L. Microvasc. Res., in press.
37. Walus, K. M., Gustav, P., and Konturek, S. J. Prostaglandins 20:1089–1102 (1980).
38. Einzig, S., Ras, G. H. R., and White, J. G. Canad. J. Physiol. Pharmacol. 58:940–946 (1980).
39. Cheung, L. Y., and Lowry, S. F. Surgery 90:291–298 (1981).
40. Miller, T. A., Henagan, J. M., and Robert, A. Dig. Dis. Sci. 25:561–567 (1980).
41. Kauffman, G. L., Jr., Aures, D., and Grossman, M. I. Amer. J. Physiol. 238:G131–G134 (1980).
42. Bill, A. Acta Physiol. Scand. 105:437–442 (1979).
43. Skarstein, A. Scand. J. Gastroenterol. 14:905–911 (1979).
44. Konturek, S. J., Mikos, E., Pawlik, W., and Walus, K. J. Physiol. 286:15–28 (1979).
45. Jacobson, E. D. Proc. Soc. Exp. Biol. Med. 133:516–519 (1970).
46. Robert, A., Nezamis, J. E., and Phillips, J. P. Amer. J. Dig. Dis. 12:1073–1076 (1967).
47. Gerkins, J. F., Shand, D. G., Flexner, C., Nies, A. S., Oates, J. A., and Data, J. L. J. Pharmacol. Exp. Ther. 203:646–652 (1977).
48. Tonnesen, M. G., Jubiz, W., Moore, J. G., and Frailey, J. Dig. Dis. 19:644 (1974).
49. Jacobson, E. D. Gastroenterology 54:434–448 (1968).
50. Konturek, S. J., Lancaster, C., Hanchar, A. J., Neyanis, J. E., and Robert, A. Gastroenterology 76:1173 (1979).
51. Wilson, D. E., and Levine, R. A. Amer. J. Dig. Dis. 17:527–532 (1972).
52. Bulkley, G. B., Perry, M. A., Kvietys, P. R., and Granger, D. N. Physiologist 24:50 (1981).
53. Shehadeh, A., Price, W. E., and Jacobson, E. D. Amer. J. Physiol. 216:386–392 (1969).
54. Granger, D. N., Scheckleford, J. S., and Taylor, A. E. Amer. J. Physiol. 236:E788–E796 (1979).
55. Nowak, J., and Wennmalm, A. Acta Physiol. Scand. 102:484–491 (1978).
56. Pawlik, W., Shepherd, A. P., and Jacobson, E. D. J. Clin. Invest. 56:484–490 (1975).
57. Balint, G. A., Kiss, Z. F., Varkonyi, T., Wittman, T., and Varro, V. Prostaglandins 18:265–268 (1979).
58. Lippton, H. L., Paustian, P. W., Sporl, L., and Kadowitz, P. J. Prostaglandins Med. 5:365–373 (1980).
59. Houwenaghel, A., and Wechsung, E. Arch. Int. Pharmacodyn. 230:332–334 (1977).
60. Chapnick, B. M., Feigen, L. P., Hyman, A. L., and Kadowitz, P. J. Amer. J. Physiol. 235:H326–H332 (1978).
61. Fondacaro, J. D., Walus, K. M., Schwaiger, M., and Jacobson, E. D. Gastroenterology 80:1542–1549 (1981).
62. Davis, L. J., Anderson, J., Wallace, S., Gianturco, C., and Jacobson, E. D. Radiology 114: 281–286 (1974).
63. Beubler, E., and Juan, H. Naunyn-Schmiedeberg's Arch. Pharmacol. 299:89–94 (1977).
64. Feigen, L. P., Chapnick, B. M., Gorman, R. R., Hyman, A. L., and Kadowitz, P. J. Prostaglandins 16:803–813 (1978).
65. Walus, K. M., Fondacaro, J. D., and Jacobson, E. D. Dig. Dis. Sci. 26:1069–1077 (1981).
66. Matuchansky, C., and Bernier, J. J. Gastroenterology 64:1111–1118 (1973).
67. Pierce, N. F., Carpenter, C. C. J., Elliott, H. L., and Greenough, W. B. Gastroenterology 60: 22–32 (1971).
68. Gallavan, R. H., Jr., and Chou, C. C. Amer. J. Physiol., in press (1982).
69. Sit, S. P., Nyhof, R., Gallavan, R., and Chou, C. C. Proc. Soc. Exp. Biol. Med. 163:273–277 (1980).
70. Aiken, J. W. Pol. J. Pharmacol.-Pharm. 26:217–227 (1974).
71. Geumi, A., Bashour, B. V., Swamy, B. V., and Nafrani, A. G. Pharmacology 9:336 (1973).
72. Nakano, J., and Cole, B. Amer. J. Physiol. 217:222 (1969).
73. Case, R. M., and Scratcherd, T. J. Physiol. 226:393–405 (1972).
74. Konturek, S. J., Tasler, J., Jaworek, J., Cieszkowski, M., and Pawlik, W. Amer. J. Physiol. G531–G536 (1980).
75. Saunders, R. N., and Moser, C. A. Arch. Int. Pharmacodyn. 197:86–92 (1972).
76. Legge, D. Clin. Radiol. 29:285–288 (1978).
77. Malik, K. U., and McGiff, J. C. In: Karum, S. M., ed. Prostaglandins Physiological, Pharmacological and Pathological Aspects. Lancaster, MTP Press, pp. 103–200, 1976.
78. Ferreira, S. H., Moncada, S., and Vane, J. R. Brit. J. Pharmacol. 47:48–58 (1973).

Received February 1, 1982. P.S.E.B.M. 1982, Vol. 170.