Prostaglandins and Renal Function: Implications for the Activity of Diuretic Agents

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Prostaglandins are primarily local or tissue hormones which act at or near their sites of synthesis and are synthesized on demand as they are not stored (1). In the kidney, as in other tissues, prostaglandins serve primarily a defensive function, although they may contribute to the maintenance of renal function under physiological conditions. Furosemide, ethacrynic acid and bumetanide, the most potent of the diuretic agents, can cause a precipitous decline in renal function, particularly in the sodium depleted subject; a prostaglandin response evoked in response to the "loop diuretic" may maintain renal function in the face of this challenge (2). The capacity of the kidney to respond to a stimulus which depresses renal function by increasing prostaglandin synthesis was first shown during administration of a vasoconstrictor agent such as angiotensin or norepinephrine (3). Release of prostaglandins coincided with restoration of renal blood flow and urine flow despite continued administration of either angiotensin II or norepinephrine.

STRESS EVOKED RENAL PROSTAGLANDIN RESPONSE

A prostaglandin mechanism seems important to the regulation of the renal circulation when the latter is compromised by an acute insult or chronic disease. For example, activation of the renin-angiotensin system by either hemorrhage (4), laparotomy (5) or a "loop diuretic" can increase synthesis of prostaglandins by the kidney; the concentration of PGE_2 in renal venous blood increased by as much as fifteen-fold during surgical stress and was closely correlated with the level of plasma renin activity (5). Thus, under acute stress the activities of the renin-angiotensin and prostaglandin systems within the kidney appear to be coupled. The contribution of a prostaglandin mechanism to the support of the renal circulation in the acutely stressed dog may be uncovered by administration of indomethacin, an inhibitor of prostaglandin synthesis (5). A large reduction in renal blood flow occurred rapidly in response to indomethacin, despite an

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attendant increase in renal perfusion pressure. There was a simultaneous decline in renal efflux of PGE_2 which was proportional to the reduction in renal blood flow. This study demonstrated that in the animal subjected to acute stress, the renal circulation was supported by a major prostaglandin component, withdrawal of which resulted in decreased renal blood flow, particularly that fraction to the inner cortex and medulla (7).

PROSTAGLANDIN RELATED EFFECTS ON RENAL BLOOD FLOW

The pattern of distribution of blood flow within the kidney may affect salt and water excretion; for example, increased blood flow to the medulla can lower the tonicity of the medullary interstitium and, thereby, diminish the capacity to concentrate urine, resulting in increased water excretion. Changes in prostaglandin synthesis, whether resulting from inhibition by aspirin-like drugs, or increases induced by either acute stress (5), infusion of arachidonic acid (8), or administration of a loop diuretic (2), are likely to be reflected primarily by alterations of that portion of renal blood flow which supplies the medulla and will be reflected by decreased or increased blood flow to the inner and mid cortex, as measured by the distribution of radioactive microspheres within the cortex. This effect of altered prostaglandin synthesis on zonal distribution of renal blood flow arises from two factors. First, stratification of prostaglandin synthetase intrarenally is opposite to that of renin; the greatest prostaglandin synthetic capacity is in the papilla and medulla, the least in the renal cortex (9). It should be noted that the apparent difference in prostaglandin biosynthetic capacity between the renal cortex and medulla may be related, in part, to the presence within the cortex of an inhibitor of cyclooxygenase (10). Second, the inner cortical and medullary circulations are continuous, as the afferent arterioles of the inner cortex extend into the medulla, giving rise to the vasa recta (11). Therefore, changes in prostaglandin synthesis in the inner medulla will have secondary effects on blood flow to the outer medulla and inner and mid cortex because of the morphological unity of these vascular structures. A possible clinical correlation of these findings is the nephropathy of analgesic abuse. Nanra et al have proposed that "analgesic-nephropathy" is due to medullary ischemia secondary to reduced synthesis of one or more vasodilator prostaglandin(s) (12), such as PGE_2 or PGI_2. Further, elevated tissue levels of PGE_2, the presumed agent of enhanced renomedullary blood flow, should result from inhibition of PGE-9-ketoreductase. Furosemide and ethacrynic acid have been shown to inhibit this enzyme and should thereby promote increased renal blood flow to the medulla (13).

The evidence for a prostaglandin mechanism participating in the regulation of the intrarenal distribution of blood flow was first obtained in the isolated blood-perfused kidney of the dog

(14) - and later in the conscious rabbit (15). One or more renal prostaglandin(s), primarily PGE_2, is responsible for mediating increases in blood flow to the renal medulla in response to stimuli as diverse as surgical trauma (5), hemorrhagic hypotension (4), salt loading (16), and loop diuretic agents (17). Those interventions which increase prostaglandin production, even though they may reduce total renal blood flow, can increase blood flow to the renal medulla. A balanced mechanism seems to regulate the distribution of renal blood flow: a prostaglandin mechanism increases blood flow to the inner cortex and medulla, and one of the components of the renin-angiotensin system, angiotensin I, probably has a major intrarenal role effecting decreases in blood flow to the medulla (18). This action on the intrarenal distribution of blood flow may be unique for angiotensin I, as angiotensin II usually results in reduction in renal blood flow to all zones (18). It should be noted that high doses of angiotensin II, which can stimulate prostaglandin synthesis, may cause an increase in medullary blood flow despite a decline in total renal blood flow. As diuretic agents have the capacity to activate the renin-angiotensin system consequent to reduction of extracellular fluid volume, some of the effects on renal hemodynamics may operate through this mechanism.

In contrast to its effect on the surgically-stressed anesthetized dog, indomethacin did not affect renal blood flow in the conscious resting dog, even in doses having major toxic effects (5). This finding supports the proposal that, under physiological conditions, those mechanisms involving renal prostaglandins are quiescent, requiring a noxious stimulus to be activated. This proposal also is in agreement with the general conclusion that prostaglandins subserve a defensive function, and that their release from an organ represents synthesis on demand, as prostaglandins are not stored (1). Although this conclusion appears valid for many tissues, it fails to explain the basal efflux, albeit low, of prostaglandins from kidneys of the conscious resting dog, which is unaffected by high doses of indomethacin (5). Further, in the conscious rabbit (15) and perhaps in resting man (19), inhibition of prostaglandin synthesis has been shown to result in increased vascular resistance. In the conscious rabbit, indomethacin increased renal vascular resistance two-fold, associated with a shift of renal blood flow to the outer cortex (15). Thus, the activity of intrarenal prostaglandin mechanisms in the conscious animal under physiological conditions may vary with the species. Nasjletti et al (20) have obtained evidence that the release of prostaglandins from the kidney under resting conditions is determined, in large part, by the activity of the renal kallikrein-kinin system.

PROSTAGLANDIN BIOSYNTHETIC CAPACITY OF RENAL TISSUES

An alternative explanation for the failure of indomethacin

to affect renal blood flow in the conscious resting dog derives from possible differences in accessibility of aspirin-like compounds to prostaglandin synthetase, perhaps reflecting variation in metabolism or distribution of the inhibitor. Another explanation is that the cyclooxygenase varies in its susceptibility to aspirin-like drugs depending on the tissue and species; this seems less likely (21). Thus, the question of access of indomethacin to its site of action, as well as species and tissue differences in the effects of indomethacin on the prostaglandin synthesizing machinery, must be kept in mind. This consideration leads to an important observation; viz., the capacity to synthesize prostaglandins is distributed widely among the cellular elements of the kidney. Cyclooxygenase is present in at least three different tissues in the kidney. The interstitial cells of the renal medulla were the first to be shown to have the capacity to synthesize prostaglandins (21). Also, cyclooxygenase was shown to be localized in the cells lining the distal nephron and collecting ducts (22); this location accords with the known interrelationships of prostaglandins and ADH (23). (Figure 1). For example, increased urinary concentrating ability in response to ADH occurred after treatment with indomethacin (24). Prostaglandins of the E series have been shown to blunt the effects of ADH (23) and favor the excretion of free water. A prostaglandin mechanism may contribute to the action of those diuretic agents which increase levels of PGE_2 in the renal medulla. The latter could be effected by an action of the diuretic agent either on synthesis of prostaglandins, or on the enzyme 15-hydroxyprostaglandin dehydrogenase which degrades PGE_2 or by inhibition of PGE-9-ketoreductase which transforms PGE_2 to $PGF_{2\alpha}$. Indeed, furosemide may have effects on each of these mechanisms; it increases prostaglandin synthesis by promoting arachidonic acid delivery to the cyclooxygenase (25) and inhibits both the dehydrogenase and reductase (13). The $NADP^+$-dependent form of the dehydrogenase has been suggested to be identical to the PGE-9-ketoreductase (26).

POSSIBLE CIRCULATING PROSTAGLANDINS

There is little evidence that prostaglandins function as circulating hormones. An exception to this was thought to be PGA_2 which, when infused intravenously, was not destroyed on passage across the pulmonary circulation (31). However, in all probability, PGA_2 is an artifact resulting from spontaneous breakdown of PGE_2 during extraction and purification of tissues or plasma; recent studies based on highly sensitive and specific mass spectrometric methods did not detect PGA_2 in the blood (32). Recently, PGI_2 has been suggested to function as a circulating hormone because its vasodepressor activity is undiminished by passage across the lung (33).

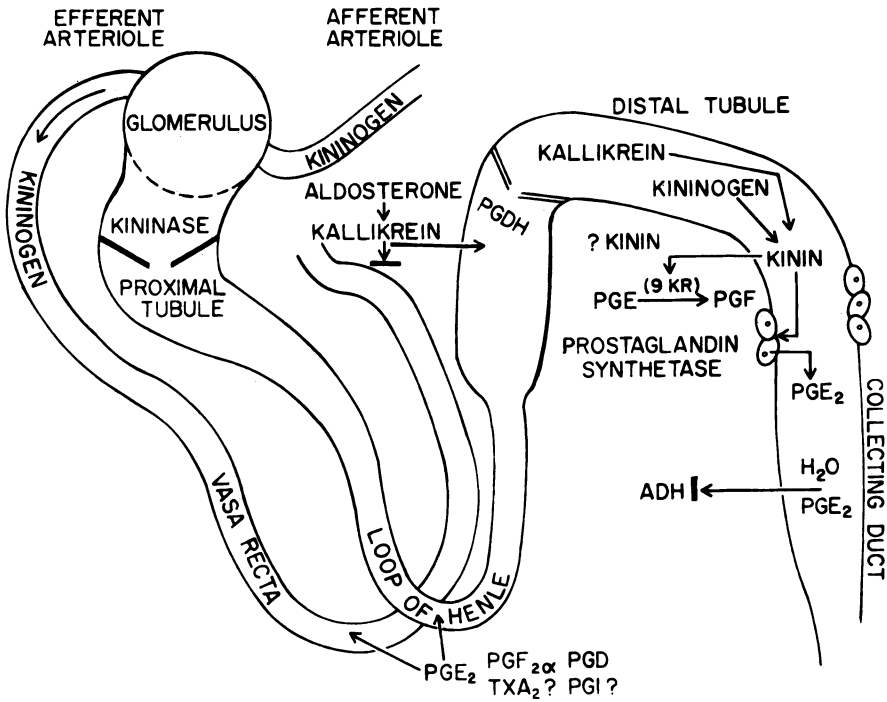

Figure 1. Prostaglandin–kinin interaction in the nephron.

The generation of kinins in the distal nephron and collecting ducts results in the release of prostaglandins which inhibit the effect of ADH and thereby participate in the excretion of solute-free water. Prostaglandin-15-hydroxydehydrogenase (PGHD), PGE-9-ketoreductase (9 KR).

RENAL ANATOMICAL COMPARTMENTS: PROSTAGLANDINS AND RENAL FUNCTION

Although cyclooxygenase is present in many tissues within the kidney, the major products of arachidonic acid metabolism, be they PGI_2, PGE_2, PGD_2, $PGF_{2\alpha}$, or TXA_2 (Figure 2), may be tissue specific and, consequently, their effects may be primarily restricted to one compartment, such as the vascular, tubular or interstitial. Thus, prostacyclin, a major product of arachidonic acid metabolism within the blood vessel wall (34), which together with other prostaglandins may affect the activity of the renin-angiotensin system, is possibly destroyed locally by the abundant prostaglandin dehydrogenases of the vascular tissues (27). The renin-angiotensin system is primarily restricted to the vascular compartment as is prostacyclin. This is in contrast to kallikrein-kinin and PGE_2 which are mainly associated with the urinary and interstitial compartments. Thus, the presence of prostaglandin synthetase within one or more cellular elements lining the urinary compartment, particularly the distal nephron and collecting ducts (22), facilitates the interaction of prostaglandins with kinins and ADH. For example, entry of kallikrein into the distal tubules, and subsequent formation of kinins, results in release of one or more prostaglandins by kinins from sites of prostaglandin generation along the collecting ducts. Inhibition of the effects of ADH can occur, then, in response to the kinin-mediated generation of prostaglandins in the distal nephron; this results in the excretion of solute-free water. A recent study by Weber et al (36) indicates that the activity of a major prostaglandin metabolizing enzyme (37), PGE-9-ketoreductase, which converts PGE_2 to $PGF_{2\alpha}$, is influenced by salt intake. Thus, reabsorption of water is facilitated by increased activity of this enzyme, which has the effect of lowering levels of PGE_2 intrarenally by favoring formation of $PGF_{2\alpha}$. As $PGF_{2\alpha}$, unlike PGE_2, does not inhibit ADH, increased activity of PGE-9-ketoreductase will facilitate reabsorption in water. The "loop diuretic" agents have already been noted to be capable of inhibiting the activity of this enzyme. It should be noted that kinins, in addition to promoting prostaglandin synthesis, are also capable of increasing the activity of PGE-9-ketoreductase (38), and that these effects may be crucial to the ability of kinins to alter excretion of solute-free water as affected by the state of sodium balance. As inhibition of prostaglandin synthesis has been shown to prevent increased free water generation induced by bradykinin (39), a prostaglandin mechanism appears to be necessary for this effect of the kinin (Figure 1).

PROSTAGLANDINS AND SALT EXCRETION

The concept of segregation of cyclooxygenases within several functional compartments of the kidney and different prostaglandins arising from these compartments is useful for

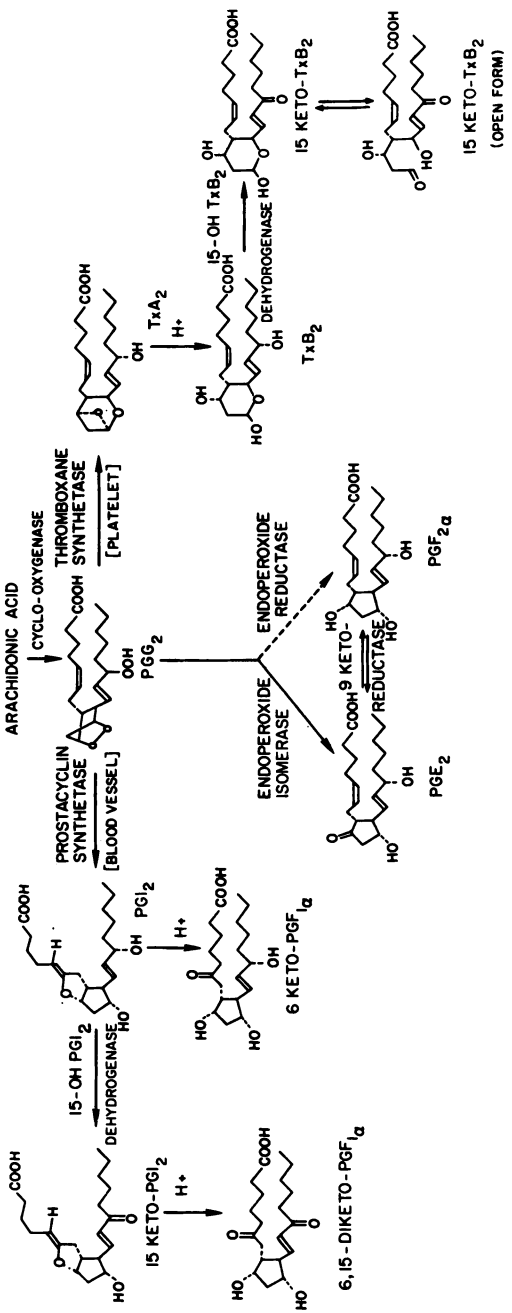

Figure 2. Metabolism of arachidonic acid by the prostaglandin synthetase complex. Major products of vascular tissues are prostacyclin (PGI_2) and PGE_2; a major product of blood platelets is thromboxane A_2 (TxA_2)

interpreting the variable effects of one or more prostaglandin mechanisms on salt excretion. The natriuretic effect of either the principal renal prostaglandin, PGE_2, or its precursor, arachidonic acid, cannot be dissociated easily from its effects on the renal circulation. In the only *in vivo* study which examined the effect of PGE_2 on tubular function uncomplicated by vascular effects, Kauker, using micro-injection techniques, demonstrated that intraluminal injection of PGE_2 in rats resulted in inhibition of sodium reabsorption (40). Further, Stokes and Kokko demonstrated an inhibitory effect of PGE_2 on sodium transport in isolated perfused renal collecting tubules of rabbits pretreated with mineralocorticoids (41). In conscious rats, Nasjletti et al (20) demonstrated that mineralocorticoid treatment not only increased kallikrein excretion, but also enhanced excretion of PGE_2 by two- to three-fold. Augmented excretion of kallikrein and PGE_2 in these rats was associated with escape from the salt and water retaining effects of mineralocorticoids. In the rat, inhibition of prostaglandin synthesis also results in increased concentration of sodium chloride in the renal medulla (42). The latter suggests that exaggerated tubular reabsorption of sodium in the ascending limb of the loop of Henle results from eliminating a prostaglandin mechanism which promotes salt excretion. On the other hand, in the conscious dog undergoing a water-induced diuresis, both indomethacin and meclofenamate have been reported to increase sodium excretion (43). A possible prostaglandin mechanism which prevents demonstration of the direct natriuretic action of bradykinin was described by McGiff et al in the blood-perfused isolated canine kidney (39). Thus, a natriuretic action of bradykinin was not shown until prostaglandin synthesis was inhibited by indomethacin. These seemingly discrepant studies may be reconciled if it is recognized that the experimental conditions determine not only the level of prostaglandin activity, but also the major species of prostaglandins produced within the urinary compartment. As these vary, the effects of indomethacin, which also alters prostaglandin metabolizing enzymes (13), will depend on the level and profile of prostaglandins produced under a given set of conditions. This, in turn, is related to the state of salt and water balance, the degree of stress occasioned by anesthesia and surgery, the activity of other hormonal systems, the "intrinsic" activity of the cyclooxygenase as determined by natural inhibitors and activators, and, finally, the species being studied. These general considerations force the conclusion that the products of cyclooxygenases in the various compartments within the kidney may vary with experimental conditions, as well as in health and in disease. For example, thromboxane, a powerful vasoconstrictor; is not normally synthesized by the kidney. However, when renal function is disturbed, as by acute ureteral ligation, thromboxane synthesis may occur (44). Its production may contribute to the late increase in renal vascular resistance in response to

ureteral obstruction (45).

Changes in extracellular potassium concentration can also affect renal prostaglandin synthesis (46). As urinary kallikrein concentrations have been positively correlated with excretion of potassium, but not sodium (47), the possibility of a potassium-dependent interaction of prostaglandins with kallikrein-kinins should be considered. Thus, induction of potassium deficiency has been shown to result in enhanced renal prostaglandin synthesis (48). Hyposthenuria associated with potassium deficiency, then, may be related to inhibition of the effects of ADH (23) consequent to increased production of PGE_2 or a related prostaglandin.

SUMMARY

Those diuretic agents such as furosemide which have as their primary sites of action the ascending limb of the loop of Henle and the cortical collecting ducts, where they have a primary effect on chloride transport (49), can be shown to have major effects not only on the renin-angiotensin system (6), but also on the kallikrein-kinin (50) and prostaglandin systems (13). There is evidence suggesting that their diuretic action may be related partially to an effect on the vasodilator-diuretic system of the kidney, the kallikrein-kinin-prostaglandin system. Thus, aspirin-like compounds have been shown to blunt the diuretic action of furosemide (51), although this effect of antiinflammatory acids is complicated by their inhibition of the organic acid secretory system. Integrity of the latter may be required for access of these diuretic agents to their active sites. Further, furosemide and ethacrynic acid have been shown to inhibit two of the major prostaglandin catabolizing enzymes, prostaglandin-15-hydroxydehydrogenase and PGE-9-ketoreductase (13). Their effects on these enzymes may result in increased levels of PGE_2 and PGI_2 which may then contribute to vasodilator-diuretic mechanisms. The design of agents which have major effects on prostaglandin metabolism is well underway and has already resulted in novel diuretic agents (52).

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Literature Cited

1. Änggard, E., Bohman, S. O., Griffin, J. E., III, Larsson, C., and Maunsbach, A. B., Acta Physiol. Scand. (1972), 84, 231-246.
2. Olsen, U. B., Acta Pharmacol. Toxicol. (1977), 41, 1-31.
3. McGiff, J. C., Crowshaw, K., Terragno, N. A., and Lonigro, A., Nature (1970), 227, 1255-1257.
4. Vatner, S. F., J. Clin. Invest. (1974), 54, 225-235.
5. Terragno, N. A., Terragno, D. A. and McGiff, J. C. Circ. Res. (1977), 40, 590-595.

6. Bailie, M.D., Davis, L. E. and Loutzenhiser, R., Am. J. Physiol (1973), 224, 425-430.
7. Itskovitz, H. D., Terragno, N. A. and McGiff, J. C., Circ. Res. (1974), 34, 770-776.
8. Chang, L. C. T., Splawinski, J. A., Oates, J. A. and Nies, A. S., Circ. Res. (1975), 36, 204-207.
9. Larsson, C. and Änggard, E., Eur. J. Pharmacol. (1974), 21, 30-36.
10. Terragno, N. A., McGiff, J. C. and Terragno, A., Clin. Res. (1978), 26, 545A (abstract).
11. Fourman, J. and Moffat, D. B., "Blood Vessels of the Kidney", p. 58, Oxford, Blackwell Scientific Publications, Oxford, England, 1971.
12. Nanra, R. S., Chirawong, P. and Kincaid-Smith, P., Aust. N. Z. Med. (1973), 3, 580-586.
13. Stone, K. J. and Hart, M., Prostaglandins (1976), 12, 197-207.
14. Itskovitz, H. D., Stemper, J., Pacholczyk, D. and McGiff, J. C., Clin. Sci. (1973), 45, 321s-324s.
15. Beilin, L. J. and Bhattacharya, J., J. Physiol. (1977), 269, 395-405.
16. Papanicolaou, N., Safar, M., Hornych, A., Fontaliran, F., Weiss, Y., Bariety, J. and Milliez, P., Clin. Sci. Molec. Med. (1975), 49, 459-463.
17. Olsen, U. B. and Ahnfelt-Ronne, I. Acta Physiol. Scand. (1976), 97, 251-257.
18. Itskovitz, H. and McGiff, J. C., Circ. Res. (1974), 34-35, (Suppl I), 65-73.
19. Wennmalm, A., IRCS (1974), 2, 1099.
20. Nasjletti, A., McGiff, J. C. and Colina-Chourio, J., Circ. Res., in press.
21. Pong, S. S. and Levine, L., J. Pharmacol. Exp. Ther. (1976), 196-197, 226-230.
22. Smith, W. L. and Wilkin, G. P., Prostaglandins (1977), 13, 873-892.
23. Grantham, J. J. and Orloff, J., J. Clin. Invest. (1968), 47, 1154-1161.
24. Berl, P., Raz, A., Wald, H., Horowitz, J. and Czaczkes, W., Am. J. Physiol. (1977), 232, F529-F537.
25. Weber, P. C., Scherer, B. and Larsson, C., Eur. J. Pharmacol. (1977), 41, 329-332.
26. Hassid, A. and Levine, L., Prostaglandins (1977), 13, 503-516.
27. Wong, P. Y-K., Sun, F. F. and McGiff, J. C., J. Biol. Chem. (1978), in press.
28. Larsson, C., Weber, P. and Änggard, E., Eur. J. Pharmacol. (1974), 28, 391-394.
29. Gerber, J. G., Branch, R. A., Nies, A. S., Gerkens, J. F., Shand, D. G., Hollifield, J. and Oates, J. A., Prostaglandins (1978), 15, 81-88.

30. Terragno, D. A., Crowshaw, K., Terragno, N. A. and McGiff, J. C., Circ. Res. (1975), 36-37, (Suppl I), 76-80.
31. McGiff, J. C., Terragno, N. A., Strand, J. C., Lee, J. B., Lonigro, A. J. and Ng, K. K. F., Nature (1969), 223, 742-745.
32. Frolich, J. C., Sweetman, B. J., Carr, K., Hollifield, J. W. and Oates, J. A., Prostaglandins (1975), 10, 185-195.
33. Armstrong, J. M., Lattimer, N., Moncada, S. and Vane, J. R., Br. J. Pharmac. (1978), 62, 125-130.
34. Moncada, S., Gryglewski, R. J., Bunting, S. and Vane, J. R., Prostaglandins (1976), 12, 715-737.
35. Carretero, O. A. and Scicli, A. G., Fed. Proc. (1976), 35, 194-198.
36. Weber, P. C., Larsson, C. and Scherer, B., Nature (1977), 266, 65-66.
37. Leslie, C. A. and Levine, L., Biochem. Biophys. Res. Commun. (1973), 52, 717-724.
38. Wong, P. Y-K, Terragno, D. A., Terragno, N. A. and McGiff, J. C., Prostaglandins (1977), 13, 1113-1125.
39. McGiff, J. C., Itskovitz, H. D. and Terragno, N. A., Clin. Sci. Molec. Med. (1975), 49, 125-131.
40. Kauker, M. L., Proc. Soc. Exp. Biol. Med. (1977), 154, 272-277.
41. Stokes, J. B. and Kokko, J. P., J. Clin. Invest. (1977), 59, 1099-1104.
42. Ganguli, M., Tobian, L., Azar, S. and O'Donnell, M., Circ. Res. (1977), 40, (Suppl I), 135-139.
43. Kirschenbaum, M. A. and Stein, J. H., J. Clin. Invest. (1976), 57, 517-521.
44. Morrison, A., Nishikawa, K. and Needleman, P., Nature (1977), 267, 259-260.
45. Yarger, W. E. and Griffith, L. D., Am. J. Physiol. (1974), 227, 816-826.
46. Zusman, R. M. and Keiser, H. R., J. Clin. Invest. (1977), 60, 215-223.
47. Zinner, S. H., Margolius, H. S., Rosner, B., Keiser, H. R. and Kass, E. H., Am. J. Epidem. (1976), 104, 124-132.
48. Galvez, O. G., Bay, W. H., Roberts, B. W. and Ferris, R. F., Circ. Res. (1977), 40, (Suppl 9), 11-16.
49. Rocha, A. S. and Kokko, J. P., J. Clin. Invest. (1973), 52, 612-623.
50. Croxatto, H. R., Roblero, J. S., Garcia, R. L., Corthorn, J. H. and San Martin, M., Acta Physiol. Latino Am. (1973), 22-23, 556-558.
51. Lee, J. B., Proc. 6th Int. Congr. Nephrol. (1975), 1, 348-354.
52. Cragoe, E. J., Jr., Schultz, E. M., Schneeberg, J. D., Stokker, G. E., Woltersdorf, O. W., Jr., Fanelli, G. M., Jr., and Watson, L. S., J. Med. Chem. (1975), 18, 225-228.

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