Prostaglandins – Tomorrow's Drugs

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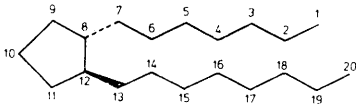
The novel structure of the prostaglandin molecule has in recent years attracted the attention of many synthetic organic chemists. Difficulties inherent in synthesizing compounds which present so many stereochemical problems offer a challenge to ingenious inventiveness, whilst the possibility of synthesizing new compounds with more selective biological activity than the natural prostaglandins opens up wide areas of practical application in both human and veterinary medicine.

The semi-systematic nomenclature[1] of the natural compounds is based upon the hydrocarbon prostane (1) and the corresponding monocarboxylic acid prostanoic acid (2). The stereochemistry at positions 8 and 12 should be noted. The first two prostaglandins to be isolated from sheep vesicular glands were named prostaglandin E and prostaglandin F by Bergström and Sjövall in 1960.[2] These compounds were later designated prostaglandin E_1 (PGE_1, 3) and prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$, 4) when analogues with additional double bonds were isolated, namely PGE_2 (5) and PGE_3 (6).[3] The subscript numerals refer in each case to the number of double bonds in the side-chains.

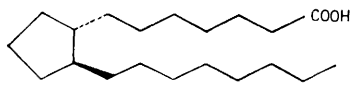
At an early stage it was shown that the PGE molecule could be converted chemically into a variety of related prostaglandins, most of which have now been found to occur naturally (Figure 1). Thus reduction with sodium borohydride gives rise to the epimers F_α and F_β. Under mildly acidic conditions the molecule is dehydrated to PGA or under more rigorous alkaline conditions to the isomer of PGA, *viz.* PGB. Naturally occurring prostaglandins comprise a number of families, each designated by a different letter (from A to H) indicating a difference in the nature of the five-membered ring. These differences may be seen in Figures 1 and 2. The two cyclic endoperoxide prostaglandins, PGG_2 and PGH_2,[4] have hydroperoxy- and hydroxy-substituents, respectively, at the 15-position.

Virtually all animal tissues contain one or other prostaglandin.[5,6] It seems likely that in most instances prostaglandins are not stored as such.[7,8] They are

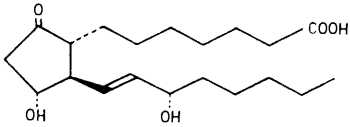
[1] N. A. Nelson, *J. Medicin. Chem.*, 1974, **17**, 911.
[2] S. Bergström and J. Sjövall, *Acta Chem. Scand.*, 1959, **14**, 1693, 1701.
[3] S. Bergström, R. Ryhage, B. Samuelsson, and J. Sjövall, *Arkiv. Kemi*, 1962, **19**, 563.
[4] M. Hamberg and B. Samuelsson, *Proc. Nat. Acad. Sci., U.S.A.*, 1973, **70**, 899.
[5] S. Bergström, *Science*, 1967, **157**, 382.
[6] E. W. Horton, 'Prostaglandins', Monographs on Endocrinology, Vol. 7. Springer-Verlag. Heidelberg, 1972.
[7] B. N. Davies, E. W. Horton, and P. G. Withington, *Brit. J. Pharmacol.*, 1968, **32**, 127.
[8] P. Piper and J. R. Vane, *Ann. New York Acad. Sci.*, 1971, **180**, 363.



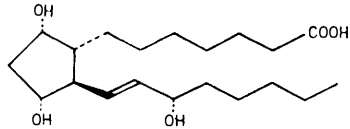
PROSTANE
(1)



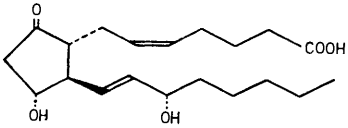
PROSTANOIC ACID
(2)



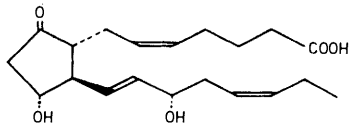
PROSTAGLANDIN E_1
(3)



PROSTAGLANDIN $F_{1\alpha}$
(4)



PGE_2
(5)



PGE_3
(6)

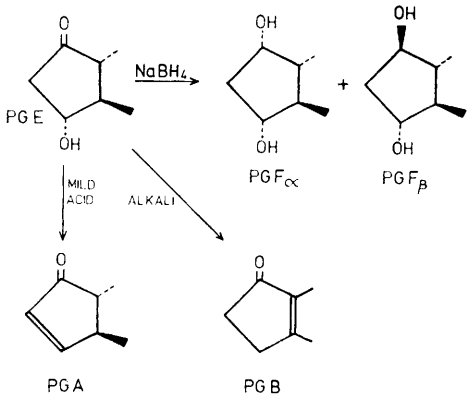
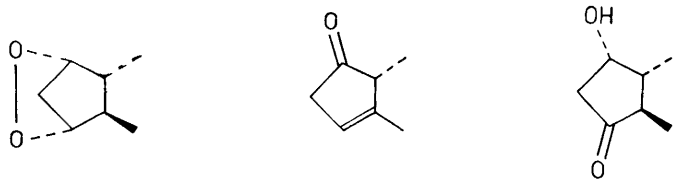


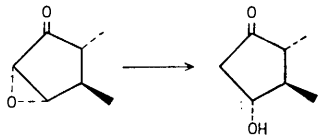
Figure 1 *Derivatives of prostaglandin E*



CYCLIC ENDOPEROXIDE PGC PGD

Figure 2 *Other prostaglandin families*

very readily formed from precursor unsaturated fatty acids in response to a variety of stimuli. In contrast, a Caribbean coral, *Plexaura homomalla*, contains vast quantities of a prostaglandin A, no less than 1.5% of its dry weight.[9] This has been an extremely important source of starting material for the synthesis of prostaglandins for clinical use. Formation of the 10,11-epoxide of PGA_2 (7) in turn leads to the production of the hydroxycyclopentanone PGE_2 (8) or its 11-epimer. A method for the stereospecific production of PGE_2 (98%) has been devised by Corey,[10] who protected the 15-hydroxy-group by forming the trixylylsilyl derivative. This allowed the preferential formation of the α-epoxide.



(7) (8)

The discovery of pharmacologically active agents of animal origin has in the past been a profitable starting point for the development of new drugs of clinical importance. For example, the discovery of histamine led to the development of the antihistamines for use in the treatment of allergies and, more recently, to the H_2-receptor blocking drugs that are of potential importance in the treatment of peptic ulcers. The discovery of adrenaline led in its turn to the development of more selective sympathomimetic agents, *e.g.* isoprenaline and salbutamol, which are of importance in the treatment of asthma, and to the synthesis of specific antagonists which block the action of adrenaline at one or other of its receptors. Thus the beta-blockers are currently of great importance in the treatment of various cardiovascular disorders. Likewise, studies on the biosynthesis of adrenaline and noradrenaline and the recognition of an intermediary, dopamine, as a substance of importance in its own right in the central nervous system, have led to the use of *l*-dopa in the treatment of Parkinson's disease and α-methyl-dopa for alleviating hypertension. Moreover, inhibition of mono-amine oxidase, one of the enzymes which inactivate the catecholamines, has also found clinical usefulness.

[9] A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Letters*, 1969, 5185.
[10] E. J. Corey and H. E. Ensley, *J. Org. Chem.*, 1973, **38**, 3187.

Various points of attack can therefore be delineated, as illustrated in the very simple diagram of Figure 3. By inhibition of biosynthesis, the formation, or excessive formation, of the natural product could be prevented. A second point of attack is inhibition of the inactivation process, leading to an accumulation of the biologically active natural product or possibly of one of its active metabolites. The third and most obvious line of attack would be to make novel compounds which act directly on the tissue receptors, these compounds being more selec-

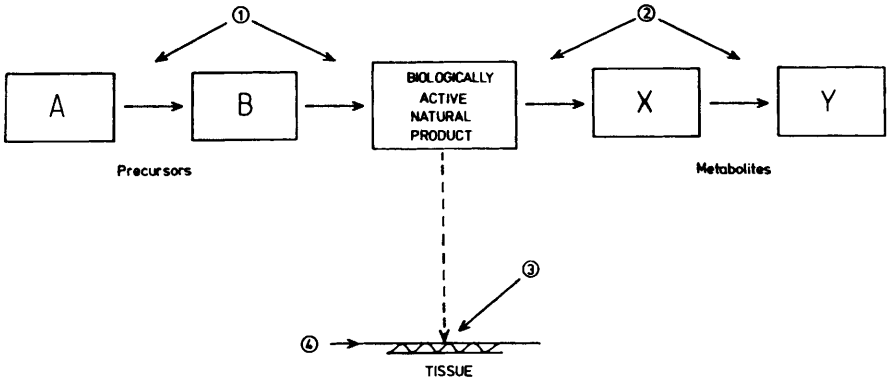


Figure 3 *Possible sites of chemical attack on a biological system.*
(1) *Inhibition of biosynthesis (or release)*
(2) *Inhibition of metabolism*
(3) *More selective action on tissue receptors*
(4) *Blockade of receptors by specific antagonists*

tive than the naturally occurring compound. This approach has been particularly fruitful in the steroid field. Finally, by synthesizing antagonists, the actions of the endogenous compound could be blocked. Again, there could well be selective antagonists which would block some, but not all, of the actions of the natural product or products at the receptor site. How far have these approaches been applied in the prostaglandin field?

What do we know of the biosynthesis of these compounds? In 1964 the enzymatic conversion of arachidonic acid into prostaglandins E_2 and $F_{2\alpha}$ was described.[11,12] The microsomal enzyme complex concerned was called prostaglandin synthetase. Free arachidonic acid itself is not found in large quantities within cells. It must be released from membrane phospholipids by the action of phospholipase A_2 (alternative sources are cholesterol esters). It is now known that there are at least three products of prostaglandin synthetase, *i.e.* PGE, PGF, and PGD (Figure 4). These prostaglandins are formed from a common precursor and are not precursors one of the other.

[11] S. Bergström, H. Danielsson, and B. Samuelsson, *Biochim. Biophys. Acta*, 1964, **90**, 207.
[12] D. A. van Dorp, R. K. Beerthius, D. H. Nugteren, and H. Vonkeman, *Biochim. Biophys. Acta*, 1964, **90**, 204.

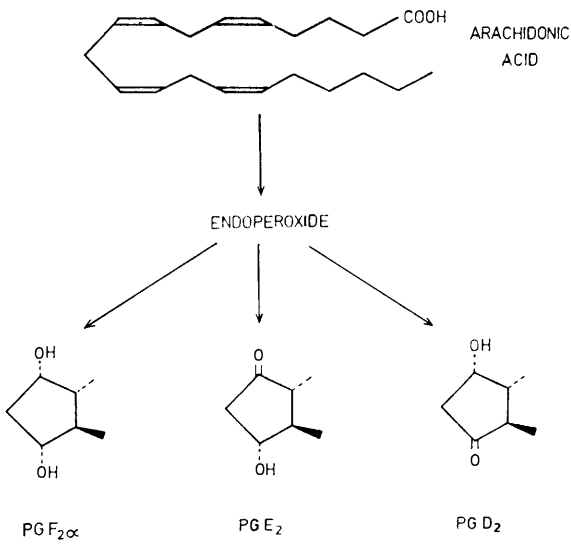


Figure 4 *Products of prostaglandin synthetase*

Various inhibitors of prostaglandin synthetase have been discovered. Van Dorp and his colleagues found that a number of unnatural analogues of the essential fatty acids would inhibit the conversion of arachidonic acid into prostaglandins.[13] Likewise, the acetylenic analogue of arachidonic acid (eicosatetraynoic acid) is a powerful inhibitor of prostaglandin synthetase.[14] Both these groups of compounds are thought to occupy the arachidonic acid site on the enzyme.[15] The most important advance resulted from the discovery in 1971, by J. R. Vane, that prostaglandin biosynthesis is blocked by aspirin and pharmacologically related compounds.[16] These drugs are not competitive inhibitors and it would seem unlikely from their chemical structure (Figure 5) that they act directly on the substrate receptor site. These compounds have now been used extensively for the investigation of the role of prostaglandins in both physiological and pathological conditions. Moreover, the discovery of their mode of action has provided a rational explanation for the way in which aspirin and other non-steroidal anti-inflammatory drugs produce their beneficial effects in man, reducing pain, inflammation, and fever.[15,17] The great chemical diversity of this group opens up the possibility of discovering more selective compounds, for

[13] D. A. van Dorp, *Ann. New York Acad. Sci.*, 1971, **180**, 181.
[14] D. T. Downing, D. G. Ahern, and M. Bachta, *Biochem. Biophys. Res. Comm.*, 1970, **40**, 218.
[15] R. J. Flower, *Pharmacol. Rev.*, 1974, **26**, 1.
[16] J. R. Vane, *Nature New Biol.*, 1971, **231**, 232.
[17] S. Ferreira, and J. R. Vane, in 'The Prostaglandins', ed. P. W. Ramwell, Plenum Press, New York, 1974, Vol. 2, p. 1.

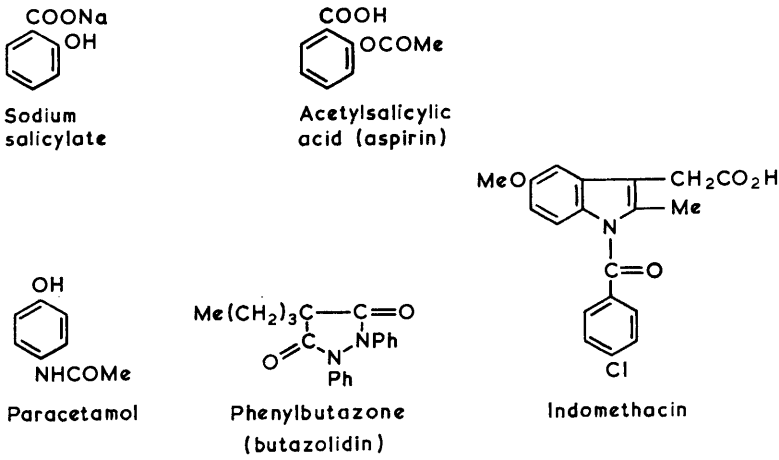


Figure 5 *Non-steroid anti-inflammatory drugs which inhibit prostaglandin synthetase*

example compounds which will block the formation of one kind of prostaglandin and not that of another. Some progress has been made towards this goal through the development of the bicycloheptenes, which block the formation of prostaglandin E but not of prostaglandin F.[18] Interestingly enough, phenylbutazone, a commonly used antirheumatic drug, appears to block PGE and PGF formation, *but not PGD*.[19] Further work in this interesting area is clearly needed.

Numerous metabolic pathways for the prostaglandins have been described (Figure 6).[20] Basically these can be divided into four groups, (*a*) oxidation of the 15-hydroxy-group by prostaglandin dehydrogenase, (*b*) reduction of the 13,14-*trans*-double bond by the 13,14-reductase, (*c*) ω-oxidation, and (*d*) β-oxidation of the α-side-chain and in some cases also of the ω-side-chain, once the dicarboxylic acid has been formed. There has been only moderate success so far in synthesizing specific inhibitors for these various metabolic enzymes.[21] The most specific enzymes for prostaglandin metabolism are the 15-hydroxy-prostaglandin dehydrogenase and the 13,14-reductase. Inhibition of these could lead to interesting biological results. It is, however, more difficult to predict any clinical usefulness for such compounds.

Analogues of prostaglandins have been synthesized which are resistant to attack by various metabolizing enzymes. For example, 3-oxo-$PGF_{1\alpha}$ (9) is

[18] P. Wlodawer, B. Samuelsson, S. M. Albonico, and E. J. Corey, *J. Amer. Chem. Soc.*, 1971, **93**, 2815.
[19] R. J. Flower, in 'Prostaglandin Synthetase Inhibitors', ed. H. J. Robinson and J. R. Vane, Raven Press, New York, 1974, p. 9.
[20] B. Samuelsson, *Ann. New York Acad. Sci.*, 1971, **180**, 138.
[21] M. A. Marrazzi, and N. H. Andersen, in 'The Prostaglandins', ed. P. W. Ramwell, Plenum Press, New York, 1974, Vol. 2, p. 99.

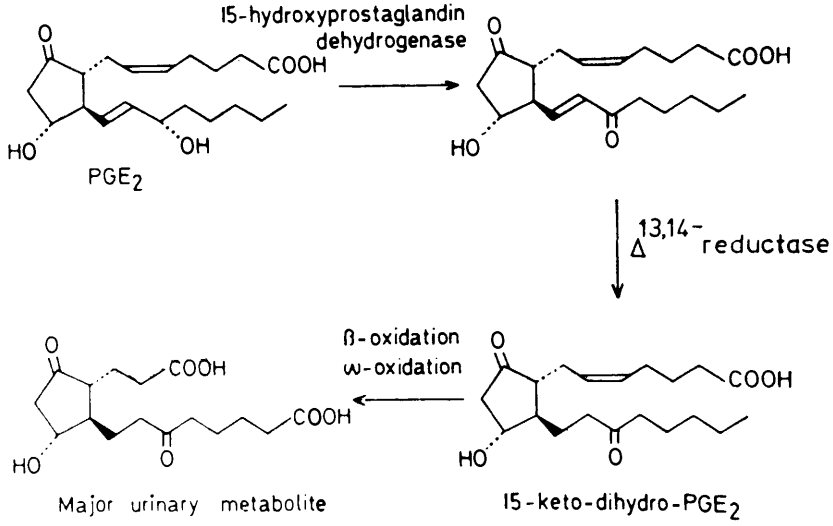
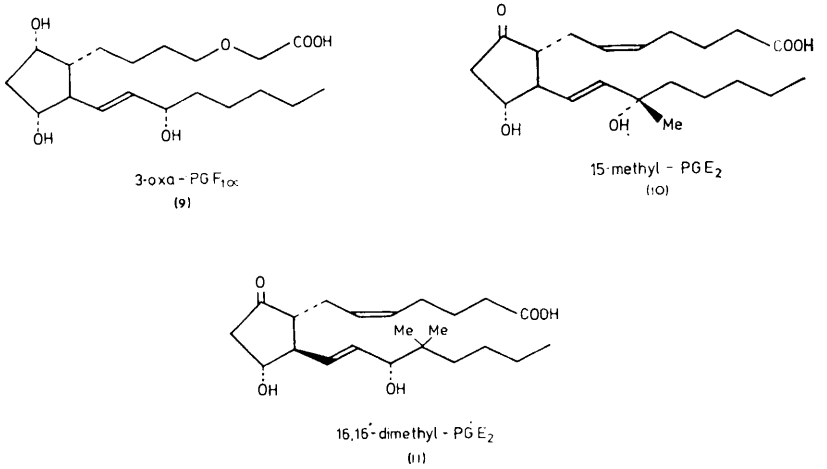


Figure 6 *Formation of the main human urinary metabolite of* PGE_2



resistant to β-oxidation.[22] Modifications which prevent the action of 15-hydroxyprostaglandin dehydrogenase have proved more profitable. Synthetic 15-methyl (10) and 16,16′-dimethyl analogues (11) are unsusceptible to oxidation at the 15-position.

[22] G. Bundy, F. Lincoln, N. Nelson, J. Pike, and W. Schneider, *Ann. New York Acad. Sci.*, 1971, **180**, 76.

The first clinical use of a prostaglandin was to induce parturition.[23] In many hospitals in the United Kingdom, PGE_2 taken orally is now used routinely in childbirth. This has many advantages over the less convenient oxytocin drip. Prostaglandins in larger doses also induce abortion.[24] Initially this was achievde by intravenous infusion of $PGF_{2\alpha}$ or PGE_2, but now the preferred method is to make a single injection of the prostaglandin directly into the uterus, either intra- or extra-amniotically. 15-Methyl-$PGF_{2\alpha}$ has proved very effective for this purpose, though it has not yet been cleared for routine clinical use.

In the middle 1960's Ramwell and Shaw discovered that prostaglandins can inhibit gastric secretion in the rat.[25] Simultaneously, Robert at the Upjohn Company carried out experiments on dogs with stomach pouches, and showed that both PGE_1 and PGE_2 administered intravenously are powerful inhibitors of the secretion of gastric juice that is secreted in response to histamine, pentagastrin, or food.[26] Unfortunately, neither of these prostaglandins is effective by mouth in man.[27] On the other hand, 16,16′-dimethyl-PGE_2 (11) is a powerful inhibitor of gastric secretion when given by mouth to normal human volunteers or to patients with peptic ulcer.[28] A single dose of 150 μg is sufficient to inhibit gastric secretion for several hours. There is now some evidence that the healing of gastric ulcers is enhanced by the administration of these compounds, and this opens the prospect of a new drug treatment for peptic ulceration.

One of the earliest observations made with the newly isolated prostaglandins E_1 and E_2 was that they relax respiratory muscle. This observation was made by Dr. Main at Miles Laboratories in England in 1964.[29] He showed that tracheal muscle is relaxed by prostaglandins of the E series and that a bronchodilator effect can also be demonstrated *in vivo*. Such results have now been extended to man, and it has been shown that aerosols of prostaglandins of the E series are about as effective as isoprenaline in causing bronchodilatation in human volunteers.[30] The prospect of using prostaglandin or prostaglandin analogues with more selective action on respiratory smooth muscle raises the possibility of a new treatment for bronchial asthma. A further interesting observation is that asthmatic patients are unusually sensitive to prostaglandin $F_{2\alpha}$, itself a bronchoconstrictor like histamine. If $PGF_{2\alpha}$ is implicated in asthmatic attacks, blockade of this compound at the receptor site by a specific antagonist could offer an alternative approach to asthma therapy.

In 1966, Kloeze, of the Unilever Company in Holland, made the remarkable observation that blood platelets *in vitro* can be prevented from aggregating by the

[23] S. M. M. Karim, R. R. Trussell, R. C. Patch, and K. Hillier, *Brit. Med. J.*, 1968, **4**, 621.
[24] S. M. M. Karim and G. M. Filshie, *Lancet*, 1970, **1**, 157.
[25] P. W. Ramwell and E. Shaw, in 'Prostaglandin Symposium of the Worcester Foundation for Experimental Biology', ed. P. W. Ramwell and J. E. Shaw, Interscience, New York, 1968, p. 55.
[26] A. Robert, in 'Prostaglandin Symposium of the Worcester Foundation for Experimental Biology', ed. P. W. Ramwell and J. E. Shaw, Interscience, New York, 1968, p. 47.
[27] E. W. Horton, I. H. M. Main, C. J. Thompson, and P. M. Wright, *Gut*, 1968, **9**, 655.
[28] S. M. M. Karim, D. C. Carter, D. Bhana, and P. A. Ganesan, *Prostaglandins*, 1973, **4**, 71
[29] I. H. M. Main, *Brit. J. Pharmacol.*, 1964, **22**, 511.
[30] M. F. Cuthbert, *Brit. Med. J.*, 1969, **4**, 723.

presence of very small quantities of PGE_1.[31] It has since been observed that prostaglandin E_1 can also inhibit platelet aggregation induced by damage to blood-vessel walls by the application of a laser beam *in vivo*. Moreover, PGD_2 is also a powerful inhibitor of platelet aggregation.[32] In contrast, PGE_2 potentiates the aggregation. Cyclic endoperoxides like PGG_2 and PGH_2 (see Figure 7) are even more powerful aggregators of platelets than PGE_2, and may be essential for aggregation to take place.[33] Inhibition of the formation of these endoperoxides by drugs like aspirin will prevent platelet aggregation and may be useful in the prophylaxis of thrombosis. Rapid developments in this exciting field can be anticipated, with important implications for cardiovascular medicine.

In 1968, Pharriss, at the Upjohn Company, made the important observation that prostaglandin $F_{2\alpha}$ is luteolytic in the rat.[34] Similar luteolytic effects with this

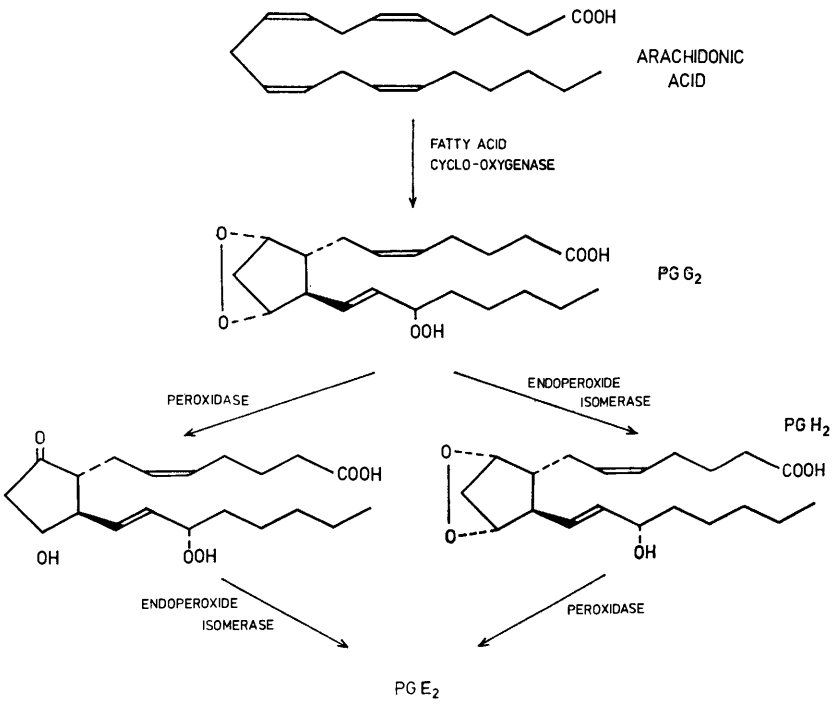
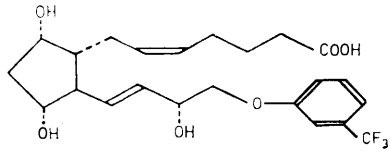


Figure 7 *Mode of formation of cyclic endoperoxides PGG_2 and PGH_2 from arachidonic acid*

[31] J. Kloeze, in 'Nobel Symposium 2: Prostaglandins', ed. S. Bergström and B. Samuelsson, Almqvist and Wiksell, Stockholm, 1967, p. 241.
[32] E. E. Nishizawa, W. L. Miller, R. B. Gorman, G. L. Bundy, J. Svensson, and M. Hamberg, *Prostaglandins*, 1975, **9**, 109.
[33] B. Samuelsson and M. Hamberg, in 'Prostaglandin Synthetase Inhibitors' ed. H. J. Robinson and J. R. Vane, Raven Press, New York, 1974, p. 107.
[34] B. B. Pharriss and L. Wyngarden, *Proc. Soc. Exp. Biol. Med.*, 1969, **130**, 92.

compound have been observed in other non-primate species, and it has now been established that in the guinea-pig, sheep, pig, and cow prostaglandins almost certainly have a physiological role as luteolytic substances.[35] They are synthesized by the uterus, and, acting locally, cause degeneration of the ipsilateral corpora lutea. Thus prostaglandin formation becomes maximal towards the end of the oestrous cycle in the guinea-pig, and this accounts for the loss of luteal function, the fall in progesterone secretion, and the initiation of a new cycle. Support for this finding has been obtained by the use of drugs which block prostaglandin formation and by immunizing guinea-pigs specifically against $PGF_{2\alpha}$. In both cases, normal cycling is interfered with. Since luteolysis is of such fundamental importance in reproduction, it is not surprising that attempts have been made to produce prostaglandin analogues with more selective luteolytic action. There has been considerable success in this field, notably by the synthesis of various compounds by the Pharmaceutical Division of Imperial Chemical Industries. An example is I.C.I. 81008 (12), which is a highly selective luteolytic substance.[36] This compound and others are now finding practical use in the veterinary field.[37] The synchronization of oestrus in cattle is of considerable commercial importance

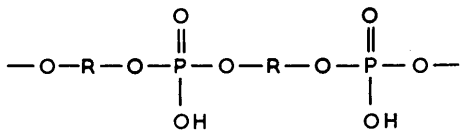


I.C.I. 81008
(12)

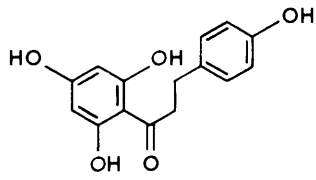
where artificial insemination is extensively used in large herds. This can now be achieved by prostaglandin treatment. Similarly, mares can be brought into oestrus on a selected day, a practice now common in the breeding of race-horses. A further use may be the induction of parturition in pigs to ensure that farrowing occurs not haphazardly but at a pre-selected time. All these new procedures involving the use of prostaglandins or their analogues have considerable economic implications.

The development of a specific prostaglandin antagonist is still in the early stages. There is some evidence that poly(phloretin phosphate) (13a) [where (13b) is the phloretin molecule] antagonizes the actions of some prostaglandins in some biological systems.[38] A much larger chemical and pharmacological effort should be devoted to this important area.

[35] E. W. Horton and N. L. Poyser, *Physiol. Rev.*, 1975, in preparation.
[36] M. Dukes, W. Russell, and A. L. Walpole, *Nature*, 1974, **250**, 330.
[37] Proceedings of the Upjohn Veterinary Symposium (1975) 'The Use of Prostaglandins in Veterinary Practice', Upjohn, Crawley.
[38] K. E. Eakins and J. H. Sanner, in 'The Prostaglandins', ed. S. M. M. Karim, Medical and Technical Publications, Oxford, 1972, p. 262.



(13a) R = phloretin



(13b)

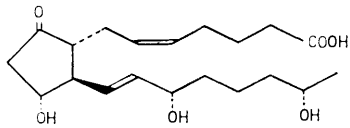
Considering then the various points of attack outlined in Figure 3, what has been achieved and what remains to be done? Inhibitors of biosynthesis have been found and many of these, of course, were already in use before it was realised that they acted in this way, for example aspirin. Virtually no inhibitors of metabolism are of practical use at the present time, though the possibility that certain diuretics act in this way is still being investigated. Considerable progress has been made in the production of more selectively active prostaglandins, notably I.C.I. 81008 and 16,16′-dimethyl-prostaglandin E_2, but little progress has been made in the attempt to find antagonists that are specific for the prostaglandin receptors.

It is clear that we require more selective rather than more active compounds for practical use in Medicine. Work with the naturally occurring prostaglandins gives some hope that it may be possible, by manipulating the molecule, to produce compounds with such selectivity. Such developments in turn may lead to the discovery of antagonists which I believe would be of considerable academic interest and clinical importance. But here too, selectivity of action would be highly desirable. There is some evidence from the work of Dr. R. L. Jones in my laboratory for the existence of more than one kind of prostaglandin receptor.[39] Antagonists which would block one but not the other, by analogy with the alpha- and beta-blocking drugs for adrenaline, would be powerful pharmacological tools.

Biologically, there are still many underdeveloped areas. For example, the role of prostaglandins in relation to the central nervous system is still hardly understood, although it is known that prostaglandins occur there, and that they have

[39] R. L. Jones, *Brit. J. Pharmacol.*, 1975, **53**, 464*P*.

some remarkable effects.[40] For example, prostaglandin E_1 inhibits leptazol convulsions in mice and prostaglandin $F_{2\alpha}$ is a potentiator of spinal reflexes. At sympathetic nerve endings prostaglandin E_2 inhibits noradrenaline release, and this may well prove to be a physiological mechanism;[41] interference with this action or mimicking it by the action of prostaglandin analogues might well have therapeutic implications in the treatment of such diseases as hypertension. The role of prostaglandins in human semen and its importance in fertility is still not understood. There is some evidence that in some infertile males there is a lower than normal content of prostaglandin E. The recent discovery by Taylor and Kelly[42] of the 19-hydroxyprostaglandin E compounds (14) in such high



(14)

concentration may well lead to further developments in this field. It is perhaps speculative to suggest that such studies could eventually lead to the development of a male 'pill'. Work on the oviduct, in which prostaglandins E have an inhibitory action,[43] is still at a very early stage. Inhibition of the various metabolic pathways, in particular, in the synthesis of arachidonic acid from dihomo-γ-linolenic acid and the interconversion of the primary prostaglandin[44] could have interesting therapeutic possibilities.

It will be apparent that the large number of natural prostaglandins that I have described in this review presents us with a field comparable in complexity to that of the steroids. Their equally diverse pharmacological activity is thought by some people to rule out the possibility of using prostaglandins in man, on the argument that a substance which does *everything* can have no usefulness. I do not share this pessimism. It is clear that there are considerable differences in selectivity of action amongst the natural prostaglandins. I believe, and this has already been amply demonstrated by I.C.I. 81008, that organic chemists can capitalize on this, and can design molecules not necessarily with more activity but with a selective action on, say, bronchial muscle for the asthmatic, gastric mucosa for the man with peptic ulcer, and the platelets or blood vessels for that vast legion of people who succumb daily to thrombosis and high blood pressure.

[40] E. W. Horton, *Physiol. Rev.*, 1969, **49**, 122.
[41] E. W. Horton, *Brit. Med. Bull.*, 1973, **29**, 148.
[42] P. L. Taylor and R. W. Kelly, *Nature*, 1974, **250**, 665.
[43] E. W. Horton and I. H. M. Main, *Brit. J. Pharmacol.*, 1963, **21**, 182.
[44] C. N. Hensby, *Biochim. Biophys. Acta*, 1974, **348**, 145.