Advances in Prostaglandin Research

Prostaglandins and Reproduction

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S. M. M. Karim

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MTP

Published by

MTP Press Ltd
St Leonard's House, St Leonardgate
Lancaster, Lancs

ISBN 0 852 00119 3

First published 1975

Printed in Great Britain by
R. & R. Clark Ltd, Edinburgh

Advances in Prostaglandin Research

This book is one of three books on the Prostaglandins edited by Professor Karim which together are designed to represent a comprehensive, critical and entirely up to date review of prostaglandin research. The contents of the other two books in the series are shown below:

Prostaglandins: Physiological, Pharmacological and Pathological Aspects

Edited by S. M. M. Karim

FUNCTIONAL CORRELATION OF THE PROSTAGLANDIN SYSTEM IN CENTRAL NERVOUS TISSUE
F. Coceani and C. Pace-Asciak

EFFECTS OF PROSTAGLANDINS ON THE AUTONOMIC NEUROTRANSMISSION
P. Hedqvist

PROSTAGLANDINS AND THE EYE
K. E. Eakins

PROSTAGLANDINS AND THE RESPIRATORY SYSTEM
A. P. Smith

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W. P. Schneider

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INHIBITION OF PROSTAGLANDIN BIOSYNTHESIS
W. E. M. Lands and L. H. Rome

PROSTAGLANDIN ANTAGONISTS
J. H. Sanner and K. E. Eakins

PROSTAGLANDIN—CYCLIC NUCLEOTIDE INTERACTIONS IN MAMMALIAN TISSUES
F. A. Kuehl, V. J. Cirillo and H. G. Olen

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Preface

This is the first in a series of three books on advances in prostaglandin research. In recent years there has been an unparalleled interest in these compounds and as a result a vast amount of research data has accumulated since the publication of my earlier book in 1972. At that time it was possible to present a fairly comprehensive review of the various aspects of prostaglandins research in one volume. This is no longer possible, and the contents are divided into three volumes: the present volume dealing with prostaglandins and reproduction and two further volumes to be published shortly dealing with other areas of prostaglandin research.

The authorship represents international scientists consisting of physiologists, pharmacologists, reproductive biologists, veterinary scientists and obstetrician gynaecologists actively engaged in different areas of prostaglandins research. Certain areas not covered in my 1972 book are included, i.e. effects of prostaglandins on the reproductive systems of the laboratory animals, (sheep and goat) and practical applications in animal husbandry. An attempt has been made to provide a total coverage of current advances relating to prostaglandins and reproduction. For the sake of completeness and continuity, material covered in my 1972 book is either briefly summarised or reference made to that edition.

The need for rapid publication in a fast expanding field is obvious. Attempts have been made to cover work published until the end of 1974 (although some omissions are inevitable) and publication date set for autumn 1975. This has only been possible as a result of the co-operation of the contributors in submitting their manuscripts on time and the efforts of the publishers in bringing out the book within a few months of receiving the manuscripts.

Tables and figures previously published are in general acknowledged by a reference in the legends and I am grateful to the respective authors, editors and publishers for their permission.

My thanks are due to my various colleagues, particularly Mr P. G. Adaikan, Drs Keith Hillier, Bhashini Rao, John Salmon and R. L. Tambyraja for discussion and advice on the subject matter of some of the chapters and to Miss Lo Pia Yong and Miss Leong Yun Kiew for cross-checking the journal references and proof reading. I am also grateful to Professor S. S. Ratnam, Head of the Department of Obstetrics and Gynaecology, University of

Singapore for his support and encouragement. I should also like to thank Miss Lily Koh for expert secretarial assistance.

Singapore, March 1975 Sultan M. M. Karim

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General Introduction and Comments

S. M. M. KARIM and B. RAO

1.1 INTRODUCTION

The last decade has been the most prolific and stimulating period in the area of prostaglandin research. The flood of information that has come out of laboratories around the world is quite staggering (Figure 1.1). This book in

itself is a witness to the vast amount of information that has accumulated in the area of reproduction alone. Such an interest in the field is exciting and augurs well for further development. However, this very fact also makes the task of the reviewer difficult.

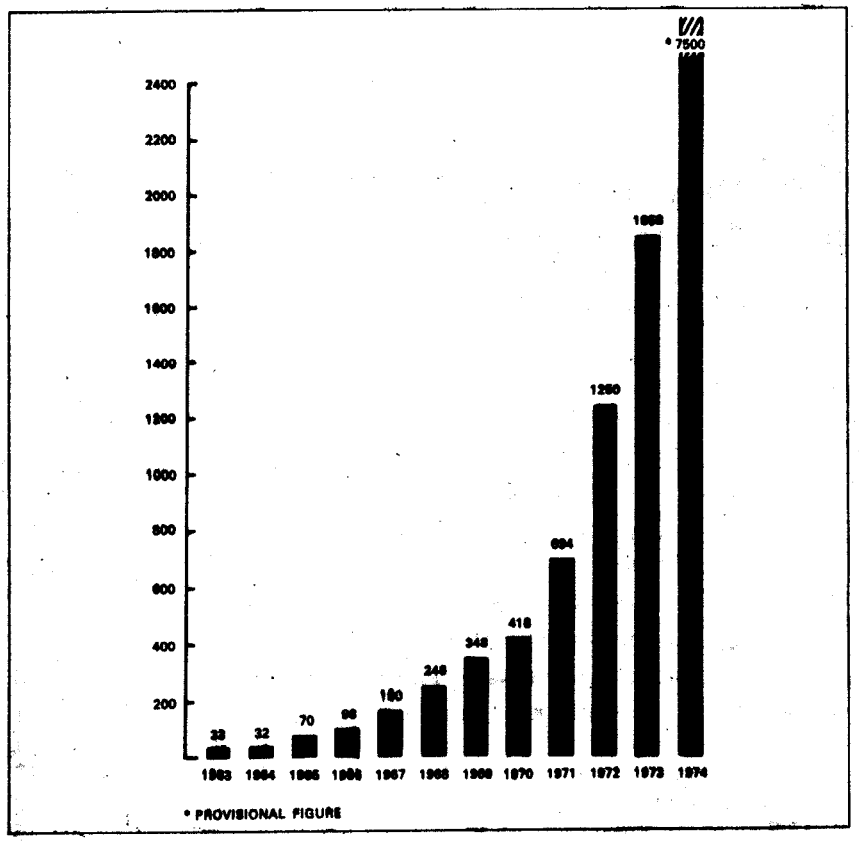

Figure 1.1 Cumulative growth of the literature in prostaglandins, 1930–1974

The increase in research activity in the field unfortunately does not seem to have brought with it a proportionate increase in the basic understanding of either the role of prostaglandins in normal reproductive processes or the basic mechanisms of their pharmacological action. Nevertheless, it has become quite evident that prostaglandins hold a key position in the common pathway through which hormones and drugs exert control over different aspects of reproduction. If the present interest in the field continues one could, with a degree of confidence, predict that what may seem at the present time to be disparate pieces of information may in fact turn out to be integral parts of the same jigsaw puzzle. Meanwhile any attempt to bring together information obtained from different experimental models (often contradictory) and to seek

some common basis must therefore seem premature. And yet it is important, at different stages of development of a field, not only to look for possible generalisations but also to a certain extent indulge in speculations since meaningful generalisation and speculation play an important role in stimulating new thoughts and in pointing to new directions. In any attempt of this kind it is difficult for the authors to completely avoid personal views and prejudices.

This chapter aims at presenting to the reader a brief overall review of historical development and the state of knowledge of the role of prostaglandins in different aspects of reproduction. Instead of merely cataloguing numerous publications an attempt is made to interpret what seems to be significant and point to the gaps in our knowledge. It is hoped that this will stimulate further research in the field.

1.2 HISTORICAL

The biological activity of seminal fluid and prostate gland extracts has been recognised for many years. Thus in ancient China seminal fluid from young adults was considered to be of therapeutic value in patients with gastric ulceration (Chau, 1972). Amongst some North African tribes oral ingestion of the father's semen is used to initiate labour when this is delayed (Harley, 1941). Pharmacological activity of prostate was first demonstrated by Japelli and Scafa (1906) who observed a rise in blood pressure of the dog upon injecting extracts of bull and dog prostate glands. In contrast aqueous extracts of human prostate gland produced a fall in blood pressure in the dog (Battez and Boulet, 1913). Kurzrok and Lieb (1930) found that fresh human semen altered the motility of the human uterus *in vitro*. A few years later Von Euler (1934, 1935) and Goldblatt (1933, 1935) independently observed the smooth muscle stimulating activity of extracts of human seminal fluid. It was Von Euler (1936) who firmly established that the pharmacological effect of the active principle in the human seminal fluid extracts was due to a completely new substance and called it prostaglandin in the belief that it was secreted by the prostate gland. Although this assumption proved incorrect when Eliasson (1959) showed that human seminal prostaglandins originate from the seminal vesicles the name prostaglandin had become firmly established. Von Euler's studies also showed that the biological activity of the seminal fluid extract was associated with a fraction containing lipid soluble acids. Similar activity was also present in the seminal fluid of the monkey, sheep, goat and extracts of sheep seminal vesicles.

1.3 PURIFICATION, ISOLATION AND CHEMICAL STRUCTURES OF PROSTAGLANDINS

After a gap of several years the work on the identification of prostaglandins was commenced in 1949 by Bergström who confirmed Von Euler's findings that the biological activity of human seminal fluid extract was due to a new group of highly active lipid soluble unsaturated hydroxy fatty acids. Bergström also recognised that seminal fluid extract contained more than one

prostaglandin. The isolation in pure crystalline form from sheep vesicular glands of the first two prostaglandins—now called prostaglandin E_1 (PGE_1 and prostaglandin $F_{1\alpha}$ ($PGF_{1\alpha}$) was reported by Bergström and Sjövall in 1957. Several related prostaglandins have since been isolated from human seminal plasma and from sheep vesicular glands and their chemical structures elucidated (see Bergström, Carlson and Weeks, 1968). The chemical structure of naturally occurring prostaglandins, their metabolites and their nomenclature have been previously discussed by Schneider (1972) and only a brief summary will be given here.

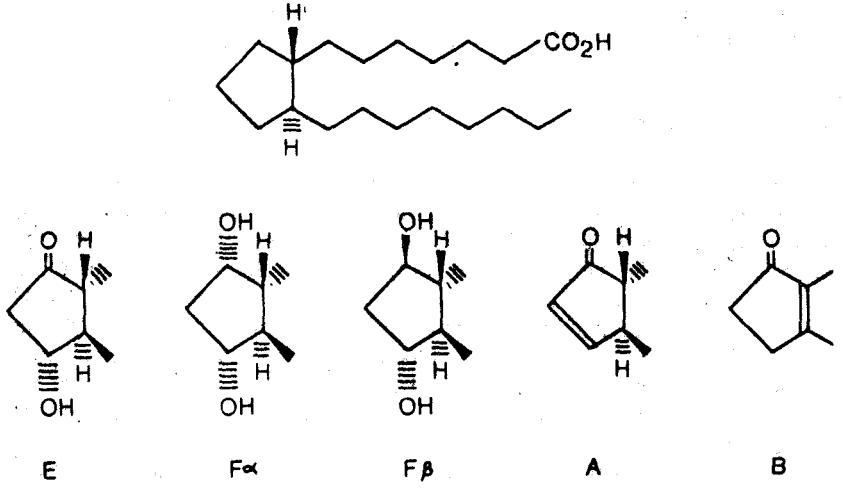

Figure 1.2 Prostanoic acid (Top) and structural differences (Bottom) between prostaglandins of the E, F, A and B series

Chemically all prostaglandins are 20-carbon hydroxy fatty acids with a cyclopentane ring and two side-chains and are derivatives of prostanoic acid (Figure 1.2). They are divided into four groups designated by the letters E, F, A and B corresponding to differences in the five-membered cyclopentane ring (Figure 1.2). The naturally occurring prostaglandin of the E and F groups (i.e. E_1, E_2, E_3, $F_{1\alpha}$, $F_{2\alpha}$ and $F_{3\alpha}$) are referred to as primary prostaglandins because other prostaglandins are derived from these compounds. All primary prostaglandins have an OH group in the 15 position and contain a 13, 14-*trans* double bond. The subscript number after the letter denotes the degree of unsaturation in the side chains of the prostaglandin molecule. Thus, PGE_1, $PGF_{1\alpha}$, A_1, B_1 have only one pair of double bonds; E_2, $F_{2\alpha}$, A_2 and B_2 have two pairs of double bonds. $F_{1\beta}$ and $F_{2\beta}$ are isomeric alcohols obtained by chemical reduction of E prostaglandins. Only the α-isomers occur naturally.

In addition to the thirteen naturally occurring prostaglandins originally reported present in the semen, Taylor and Kelly (1974) have shown that fresh human semen also contains 19-hydroxylated PGE_1 and PGE_2 (Figure 1.3). Intermediate groups of prostaglandins (intermediate between Es and Bs) of a generally unstable nature have also been identified.

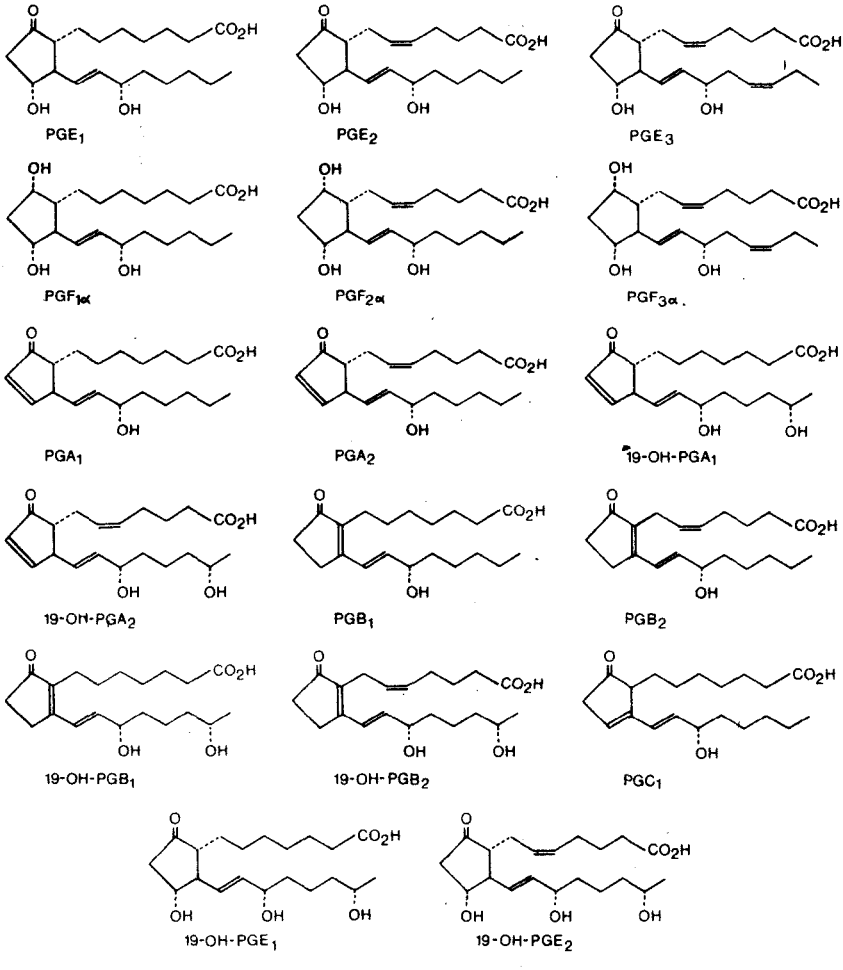

Figure 1.3 Chemical structures of naturally occurring prostaglandins

1.4 BIOSYNTHESIS AND SYNTHESIS

The precursors for the biosynthesis of prostaglandins are three unsaturated acids, e.g. 8,11,14-Eicosatetranoic acid (di-homo-γ-linoleic acid), 5,8,11, 14-Eicosatetraenoic acid (arachidonic acid) and 5,8,11,14,17-Eicosapentaneoic acid. These precursor acids are derived from the essential fatty acid—linoleic acid. Natural synthesis of prostaglandins from their fatty acid precursors is under the control of a microsomal synthetase system (prostaglandin synthetase). The pathways are outlined in Figure 1.4. Prostaglandin synthetase activity has been demonstrated in a large number of organs and this activity is inhibited by non-steroidal anti-inflammatory drugs such as aspirin, indomethacin and fenamates. Several different routes of total synthesis

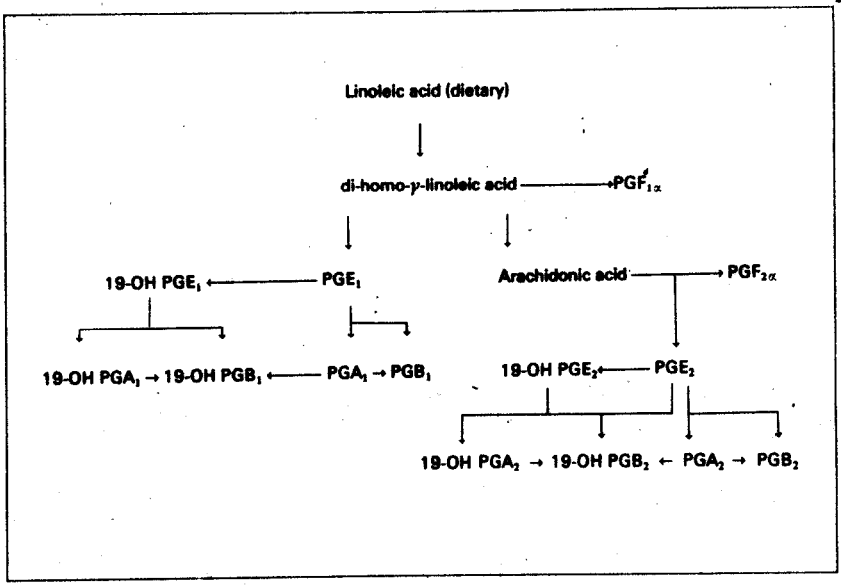

Figure 1.4 Outline of prostaglandin biosynthesis from linoleic acid

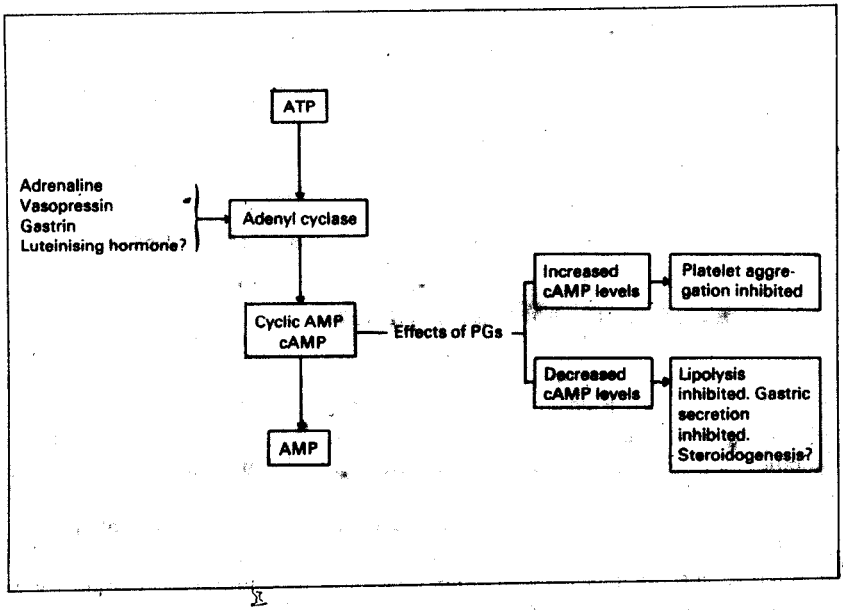

Figure 1.5 Schematic representation of prostaglandins with cyclic AMP system

Table 1.1 Occurrence of prostaglandins in human tissues and fluids

Source	*Prostaglandins*	*References*
Seminal fluid	E_1, E_2, E_3, $F_{1\alpha}$, $F_{2\alpha}$ A_1, A_2, B_1, B_2, 19-hydroxy A_1, 19-hydroxy A_2, 19-hydroxy B_1, 19-hydroxy B_2, 19-hydroxy E_1, 19-hydroxy E_2	Chapter 2
Menstrual fluid Endometrium	E_2, $F_{2\alpha}$	Chapter 2
Amniotic fluid during pregnancy and labour	E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$	Chapter 2
Maternal blood during gestation and labour	$F_{2\alpha}$, E_2	Chapter 2
Decidua	$F_{2\alpha}$, E_2	Chapter 2
Fallopian tube	$F_{2\alpha}$, E_2	Chapter 2
Umbilical and placental blood vessels	E, F	Chapter 2
Umbilical cord blood	$F_{2\alpha}$	
Aqueous humour	E_2	Wyllie and Wyllie (1971); Podos *et al.* (1972); Eakins *et al.* (1973)
Blood (normal)	$F_{2\alpha}$, E, A, F	Unger *et al.* (1971); William (1971); Jubiz *et al.* (1972); Wolfe *et al.* (1972); Jaffe *et al.* (1973); Hennam *et al.* (1974); Pletka and Hickler (1974)
Urine	$F_{1\alpha}$, $F_{2\alpha}$, E_1, E_2	Frölich *et al.* (1973)
Gastric juice and gastric mucosa	E_2	Bennett *et al.* (1968, 1970, 1973); Peskar *et al.* (1974)
Eccrine sweat	E_2	Frewin *et al.* (1973); Förström *et al.* (1974)
Kidney	A, E	Vance (1973)
Skin perfusate (normal)	E_1, E_2, $F_{1\alpha}$, $F_{2\alpha}$	Greaves *et al.* (1971)
Lung	E_2, $F_{2\alpha}$	Änggard (1965); Karim *et al.* (1967)
Thymus	E_2	Karim *et al.* (1967)
Thyroid	E_2, $F_{2\alpha}$,	
Vagus nerve	E_2, $F_{2\alpha}$,	
Cervical sympathetic nerve	E_2, $F_{2\alpha}$,	
Bronchi	E_2, $F_{2\alpha}$,	
Cardiac muscle	E_2	
Gingival tissue	E_2	Goodson *et al.* (1974)
Cells in tissue culture: epidermal, fibroblasts	E	Jaffe *et al.* (1973); Förström *et al.* (1974b)
Cerebrospinal fluid	$F_{2\alpha}$	La Torre *et al.* (1974)

of prostaglandins have been worked out and most of the presently used prostaglandins are prepared by total synthesis.

The Gorgonian plexaura homomalla is the richest natural source of prostaglandins. This Caribbean coral contains 15-epi-PGA_2 and its diester in amounts of 0.2 and 1.3% respective of the dried cortex. The coral prostaglandins have been used as intermediates to prepare biologically active natural prostaglandins and their synthetic analogues (Weinshenker and Andersen, 1973; Schneider, 1975).

1.5 DISTRIBUTION OF PROSTAGLANDINS

Prostaglandins are widely distributed in mammalian tissues, although with considerable qualitative, quantitative and species variation (Table 1.1). Their possible occurrence in tissues of lower animals and in plants is being investigated. Since the most abundant free fatty acid in the body is arachidonic acid, the majority of tissues contain either PGE_2 or $PGF_{2\alpha}$ or both. Unlike many other biologically active substances prostaglandins are formed immediately prior to release and are not stored in the body. Biosynthesis and release of prostaglandins from tissues occur so readily in response to a variety of physiological and pathological stimuli that it would appear that any distortion of cell membrane is an adequate trigger mechanism. The ease with which prostaglandins are biosynthesised implies that prostaglandin concentration values reported for many tissues do not accurately reflect the true endogenous concentration. Experimentally induced release may indicate accelerated biosynthesis rather than activation of release mechanism.

1.6 PHARMACOLOGICAL ACTIONS OF PROSTAGLANDINS

The various biological actions of prostaglandins on the tissues of male and female reproductive systems are discussed in detail in the chapters that follow. Beyond this, prostaglandins have a wide range of pharmacological actions. This is illustrated in Table 1.2 which lists in a general way some of the many actions of prostaglandins. Generally but not invariably the individual prostaglandins of a group have the same biological action on any one system but can differ quantitatively. However, the same prostaglandins may have qualitatively dissimilar effects upon different tissues and likewise prostaglandins from separate groups may have dissimilar actions. Thus PGE_1 relaxes the umbilical blood vessels *in vitro* whereas PGE_2 has a stimulant action. Prostaglandins E_1 and E_2 are bronchodilators whereas $PGF_{1\alpha}$ and $F_{2\alpha}$ induce bronchoconstriction. The prostaglandin type, the tissue, or species can determine the pharmacological or physiological effect.

Certain target organs are keenly sensitive to the prostaglandins. For instance, although over 90% of PGE and PGF compounds are metabolised during one circulation through the lungs and liver only minute doses are required to selectively stimulate human uterine muscle *in vivo*. While the actions of the prostaglandins are limited by their rapid inactivation, it has recently been shown that certain of their breakdown products which are more