THE VALUE OF PROSTAGLANDINS IN INFANCY AND CHILDHOOD

ESSAY

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BY

Saad Mahmoud El-Sayed Hassouna

MB. B. CH.

Supervised by

Dr. Mohamed Fouad Badrawi

Assistant Professor of Pediatrics

Faculty of Medicine

Ain Shams University

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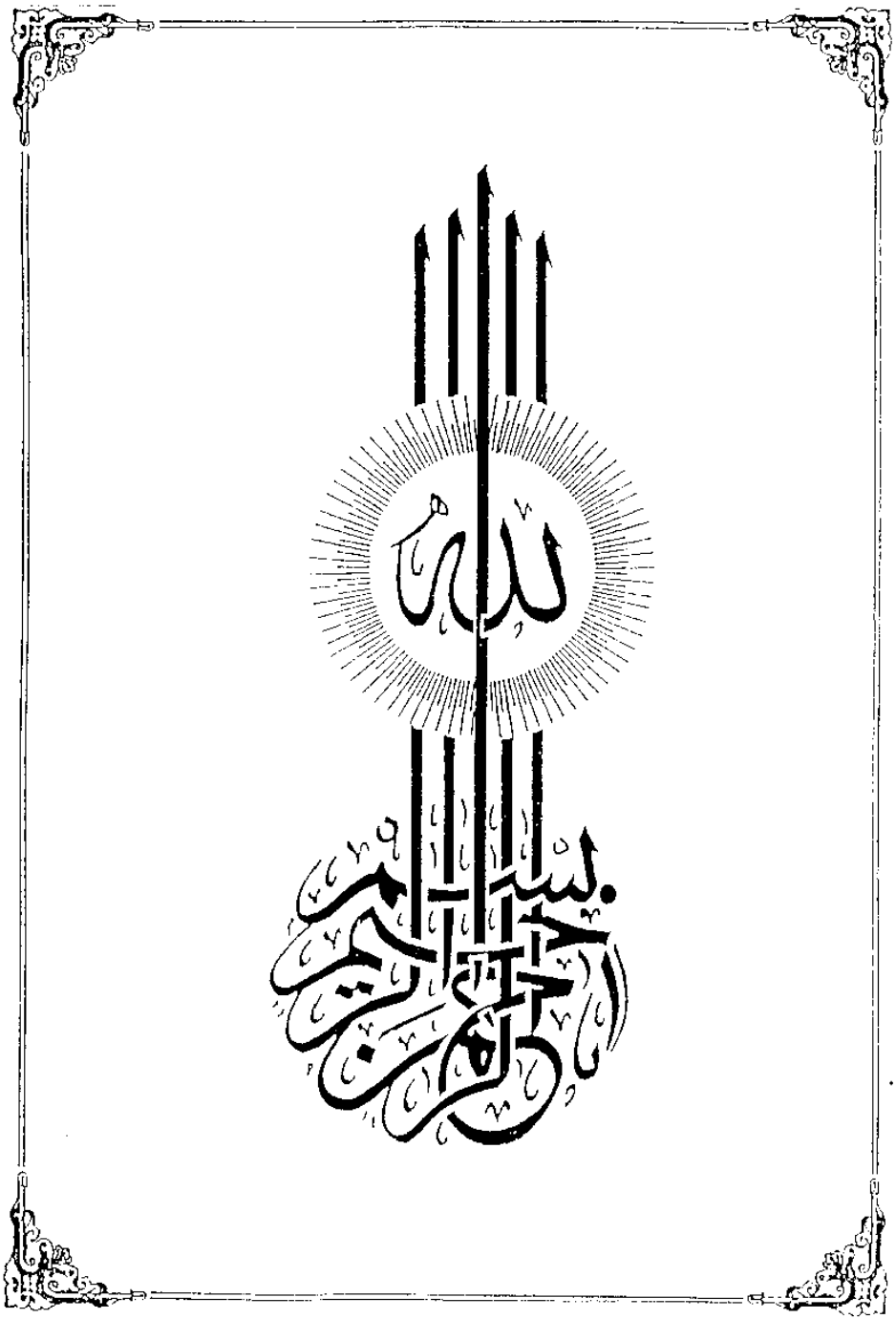
In short to all of the above mentioned, I wish to quote :

" More is thy due than more "
than all can pay.



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INTRODUCTION

The prostaglandins are a unique group of cyclic fatty acids with vast and potent biologic effects involving almost every organ system in a variety of species including the human. Biologic activity ascribable to these compounds was first discovered in the early 1930s independently by Kurzrok and Lieb, Goldblatt, and Von Euler, who observed that extracts of seminal vesicles or human semen caused contraction of the isolated uterus and lowering of blood pressure. (Lee, 1981).

The first prostaglandins identified were PGE_2, $PGF_{2\alpha}$ PGA_2, PGB_2, PGC_2 and PGD_2. These prostaglandins are referred to as the classic prostaglandins. In the course of studies on blood platelet prostaglandin synthesis, a powerful vasoconstrictor substance with platelet aggregation properties was discovered in 1975 and named thromboxane. Subsequent research has shown that prostaglandins are synthesized in virtually all cells of the mammalian organism and participate in many physiological functions.

Prostaglandins play an important role in platelet aggregation, renal incretory and excretory function, parturition, inflammation, and fever. This wide spectrum

of activites is one of the reasons that prostaglandins are of such general interest. (Frölich and Margolius, 1981).

The discovery of an unstable substance which was named PGX in 1976 and which is later named prostacyclin has been fundamently altered the understanding of thrombosis and haemostasis and opened up new therapeutic avenues, for prostacyclin itself, for stable analogues and for agents which block or divert the biosynthetic pathways of prostaglandins and thromboxanes. (O'Grady, 1980).

The latest addition to the family tree of prostaglandins, the leukotrienes, were described in 1979. These compounds are involved in the inflammatory process. (Frölich and Margolius, 1981).

Aim of the work

In this piece of work a modest trial is carried out to give a review of the current concepts of prostaglandins, their metabolism, their implication in the physiological and pathological body responses in the various systems of the body, and their role in therapy in infancy and childhood by themselves, their synthetic analogues, or through their inhibition or enhancement.

ABBREVIATIONS

AA = Arachidonic acid

ADH = Antidiuretic hormone = VP.

ADP = Adenosine diphosphate.

ATP = Adenosine tri-phosphate.

C = Carbon

CAMP = Cyclic adenosine monophosphate.

CGMP = Cyclic Guanosine monophosphate

DTS = The dense Tubular system

GFR = Glomerular filteration rate.

HETE = 12-hydroxy arachidonic acid

HPETE = 12-hydroxy-peroxy-arachidonic acid

INF = interferon

KKS = Kallekrin-Kinin system

LT = Leukotriene

NSAIDS = Non steroidal anti-inflammatory drugs.

P_8 = Picogram

PG = Prostaglandin

PGI_2 = Prostacyclin = Prostaglandin I_2

PGS = Prostaglandins

PG_2S = Prostaglandins with 2 double bonds series

R-A = Renin-Angiotensin system

RAAS = Renin-angistensin - aldosterone system

(Cont.)

SCCS = The surface connected canalicular system

SRS-A = Slow reacting substance of anaphylaxis

TSH = Thyroid stimulating hormone.

TRH = Thyrotrophic releasing hormone

TX = Thromboxane

VP = Vasopressin = ADH

BIOCHEMICAL ASPECTS OF PROSTAGLANDINS

BIOCHEMICAL ASPECTS OF PROSTAGLANDINS

CHAPTER 1

NOMENCLATURE AND STRUCTURE

The term prostaglandin in the chemically correct sense refers only to compounds derived from prostanoic acid, a chemical not found in nature. Biologists, however generally include in the definition all the compounds shown in Figure (1). The classical prostaglandins PGA_2, PGB_2, PGD_2, PGE_2 and $PGF_{2\alpha}$ are all derived from prostanoic acid and differ by virtue of functional groups on the cyclopentane ring Fig. (2). They are further categorized as mono-, di-, or tri-unsaturated according to the number of carbon-carbon double bonds, with the subscript 1 denoting a double bond between C-13 and C-14, 2 denoting an additional double bond between C-5 and C-6 and 3 denoting a third double bond between C-17 and C-18. The formulas for PGE_1, PGE_2 and PGE_3 are given in Fig. (3). (Frolich and Margoluis; 1981).

Prostaglandins derived from 8, 11, 14-eicosatrienoic acid carry the subscript 1; those derived from arachidonic acid carry the subscript 2; and those derived from 5, 8, 11, 14, 17-eicosapentaenoic acid carry the subscript 3.

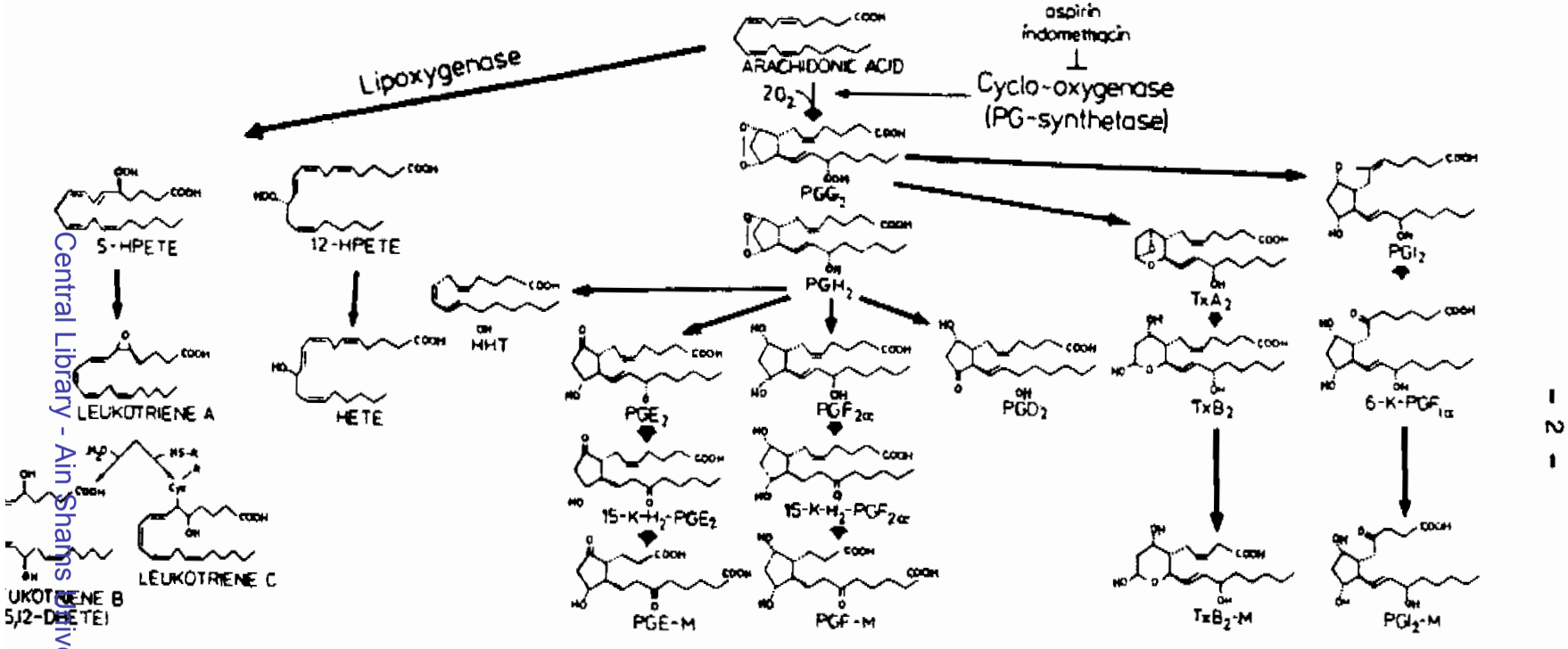


Fig. 1: Synthesis and metabolism of prostaglandins.
5-HPETE=5-hydroperoxy-6,8,11,14-eicosatetraenoic acid. 12-HPETE =12-hydroperoxy-5,8,11,14-eicosatetraenoic acid. HETE =12-L-hydroxy-5,8,10,14-eicosatetraenoic acid. HHT = 12-hydroxy-5,8,10-heptadecatrienoic acid. 6-K-$PGF_{1\alpha}$=6-Keto-$PGF_{1\alpha}$. 15-K-H_2-PGE_2=15-keto-13,14-dihydro-PGE_2. 15-K-H_2 $PGF_{2\alpha}$ = 15-keto-13,14-didhydro-$PGF_{2\alpha}$. PGE-M = 7α-hydroxy-5,11-diketotetranorprosta-1,16-dioic acid. PGF-M=5,7-dihydroxy 11-ketotetranorprosta-1,16-dioic acid. TxB_2-M dinor-TxB_2. PGI_2-M= dinor-6-Keto-$PGF_{1\alpha}$.
(Frolich and Margolius; 1981).

Fig. (4). In man, aracidonic acid is the most abundant precursor, and there is little evidence that prostaglandins of the 1 or 3 series are important. (Moncada, Flower, and Vane; 1980).

Prostaglandins, discovered initially in the seminal plasma, are synthesized in every tissue of the body. They are ubiquitous. The seminal plasma PG's are formed in the prostate gland from which the name prostaglandin is derived. PG's are rapidly synthesized as well as inactivated and the catabolizing enzymes are distributed throughout the body. In particular, the lungs not only participate in the active synthesis of PG's but also play a major role in the catabolism of PG's released into the circulation from other organs. (Bhagavan; 1978). PG's are 20-carbon derivatives of a " parent " acid, prostanoic acid which is an unnatural compound with the following structure as shown in the following page (Moncada et al, 1980). (Harper et al., 1977).

Differences between various PG's are due to substituents and their configuration on the five-membered ring. Names given to the various PG's in order to differentiate them from one another consists of PG followed by a letter (e.g. PGE, PGF, etc) and a numerical subscript

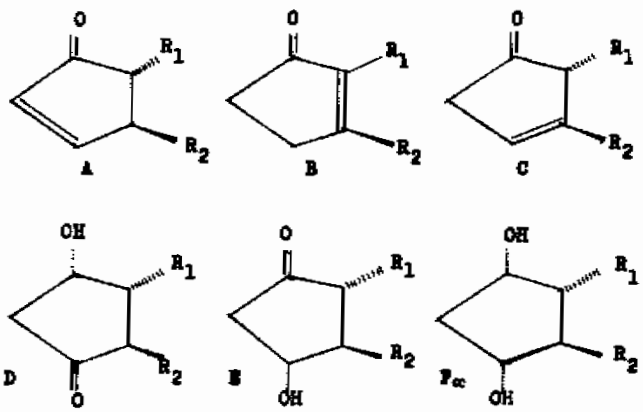
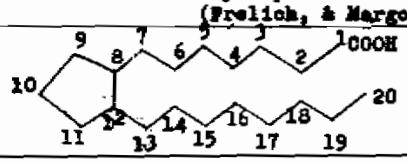


Fig.2: Structure of the cyclopentane ring of various prostaglandins (Frolich, & Margolius 1981).



Structure of prostanoic acid (Harper et al.(1977); Moncada et al.1980).

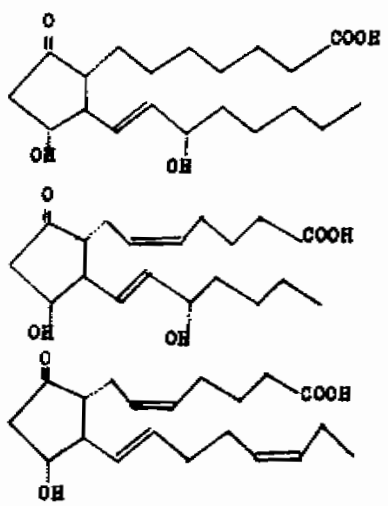


Fig.3: Structures of PGE_1, PGE_2 and PGE_3. (Frolich & Margolius 1981).

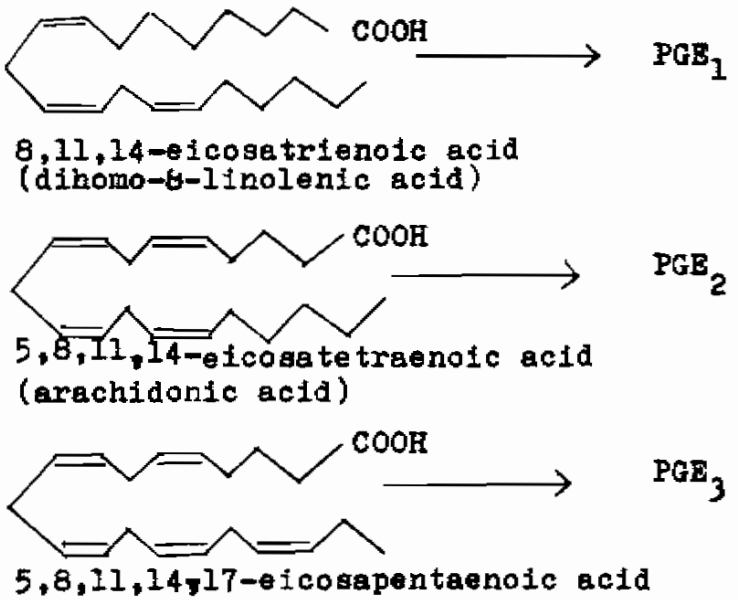


Fig.4: Prostaglandin precursors.
(Land, 1980)

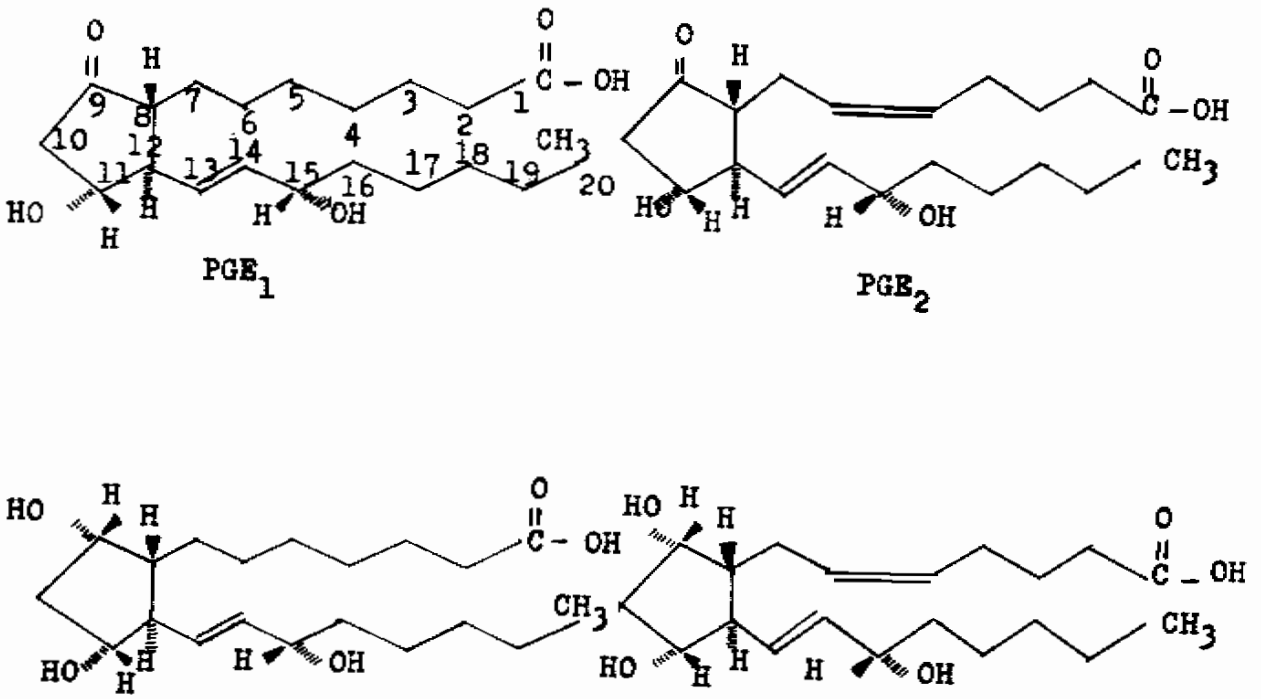


Fig.5: Structure of prostglandins E and F
(Lee, 1981)