THE PROSTAGLANDINS

THESIS

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By

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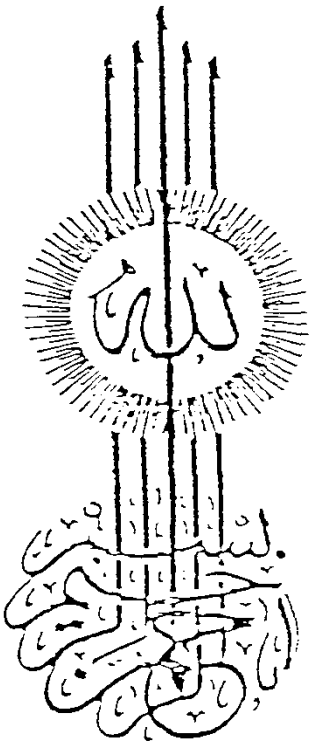

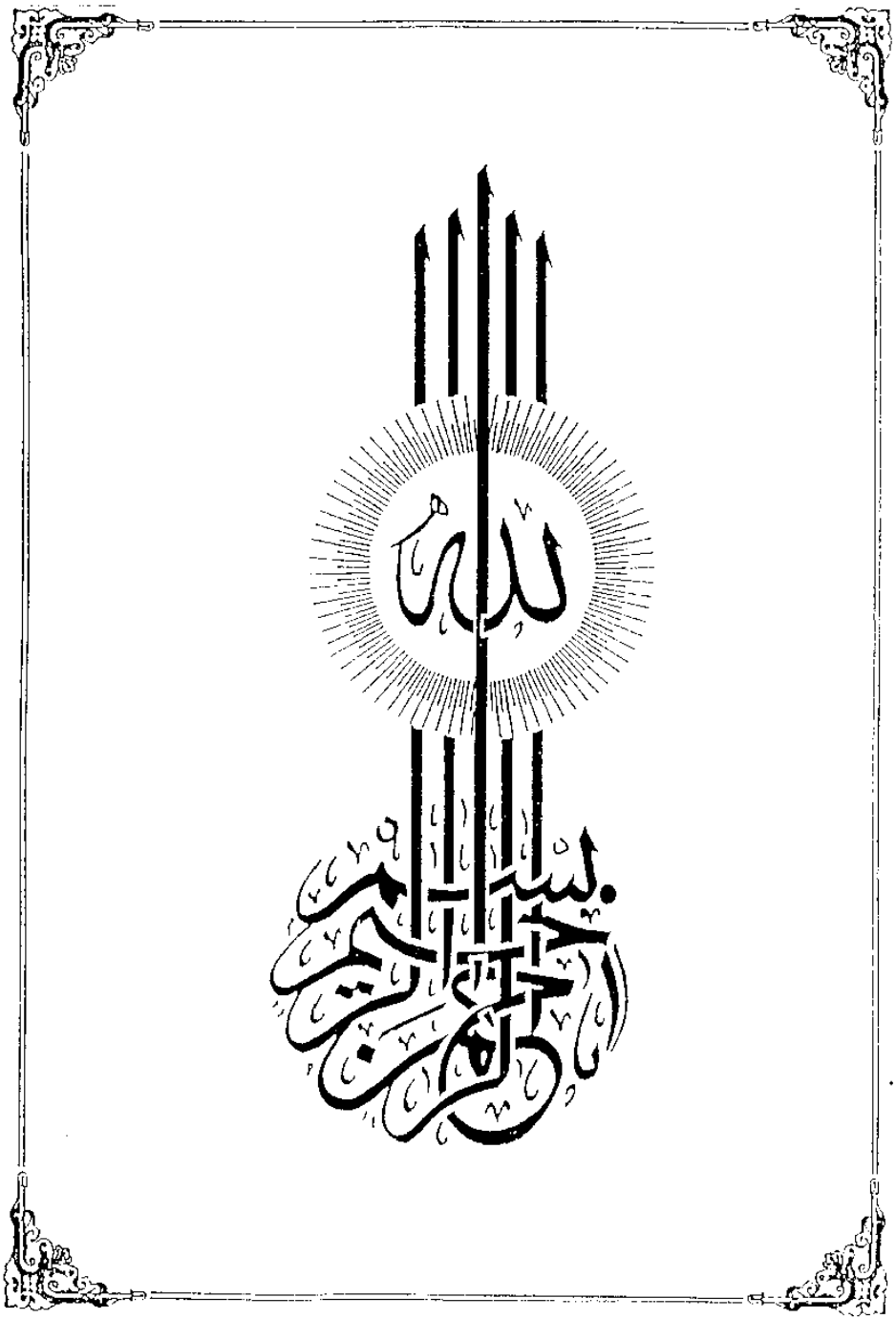

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INTRODUCTION

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There are few substances that currently command more widespread interest in biological media than do the prostaglandins, the reasons being not hard to find; they are formed by almost every animal cell studied, ranging from invertebrates to man, and from nerve cells to blood platelets. Prostaglandins are not stored, probably except in the seminal vesicles, but they are synthesized de novo in response to astonishingly diverse stimuli. When formed, they act locally at their site of biosynthesis and exert, even in trace amounts, a wide range of biological effects which might be stimulatory, inhibitory or modulatory. They are called "ubiquitus autacoids".

The history of prostaglandins goes back to 1930, when two American gynaecologists (Kurzrock and Leib, 1930) observed that fresh human semen when incubated with human myometrium slices caused either their strong contraction or relaxation depending on the reproductive history of the patients. A few years later, Goldblatt (1933) and Von Euler(1936), independently reported the smooth muscle contracting and vaso-depressor activity in the fluid and the accessory reproductive glands, and indentified the active principal as an acid lipid. Von Euler, believing this lipid to be produced in the prostate gland, he named it prostaglandin.

Latter, Elliason (1959) demonstrated that prostaglandin in human semen in fact derives from the seminal vesicles " Visiglandin". Still they are know as prostaglandins.

Years of research were to pass, during which prostaglandins were identified as a family of compounds and not a single one, and two of them were isolated in crystalline forms; being separated by differential partitioning between ether (E) and phosphate buffer(F: from Swedish; fosfat), they were named by Bergström and his group; prostaglandin E and F. Latter their structure was indentified and more prostaglandins were characterized in and outside the reproductive system. Being present in every studied tissue, they were described as "ubiquitus" (Bergström et al, 1968).

In parallel with these biochemical developments, pharmacological studies have shown the variable effects on different tissues and systems both in vitro and in vivo. Many substances of acidic lipid nature; vesiglandin, darmstoff, irin, medullin, and menstrual stimulant; were recognized to be prostaglandins (Horton, 1972).

The prostaglandins of the E, F and D series were recognised as the "partent" prostaglandins or the " primary" ones, and were considered as the predominant biologically active members of the family, untill Thromboxane A_2 and prostacyclin were identified several years ago, respectively by Hamberg et al., (1975) and Moncada et al., (1976), both of them had

dominated this area of research since the discovery was made because of their particularly Potent effects on platelet aggregation and blood vessels-tone (McGiff, 1981).

Just like prostaglandins attracted the attention of the scientific media less than 20 years ago; a new group of compunds, originating from the same fatty acid source as prostaglandins but through a different pathway called " Leukotrienes" will predictably cause the same ringing. They rival prostaglandins in their complexity and diversity (Samuelsson et al., 1980; McGiff, 1981).

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

PART I

(Biochemical Aspects)

I- STRUCTURE AND NOMENCLATURE

Prostaglandins (PGs) are a group of structurally related unsaturated fatty acid derivatives orginating, structurally, from a hypothetical parent compound called "prostanoic acid", the structure of which is shown in (fig.1); a 20-carbon, unsaturated, hydroxy fatty acid with a cyclopentane ring at C8-C12, and to which are attached two straight side chains at position 8 and 12, one of them bears the carboxyl group at its terminal end. Individual members of the family are distinguished by the number, type, and arrangement of oxygen functions and double bonds which are built upon the skeleton of the basic structure.

According to the constituents of the cyclopentane ring, PGs are classified into six main classes referred to by the capital letters A, B, C, D, E, and F; they are illustrated in (fig.2). Although all of them were isolated and studied, some of them are doubted to be existing in nature and are suggested to be artifacts of the extraction procedure, hence, PGs E, F and D are currently referred to as the parent of primary PGs, although the name was earlier attributed to the earliest isolated ones.(McGiff, 1981; Feigen and Hyman, 1981). PGE contains a keto group at position 9, while PGF has a hydroxyl group in the same position.

A subscript numeral is added after the "capital letter " to indicate the number of double bonds in the straight

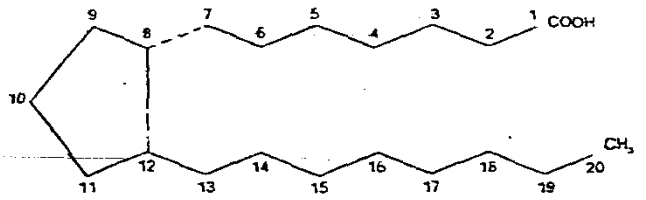

Figure 1: Prostanoic acid. The basic structure of a fully saturated 20-carbon acid, with C8-C12 closed to form a five-member ring.

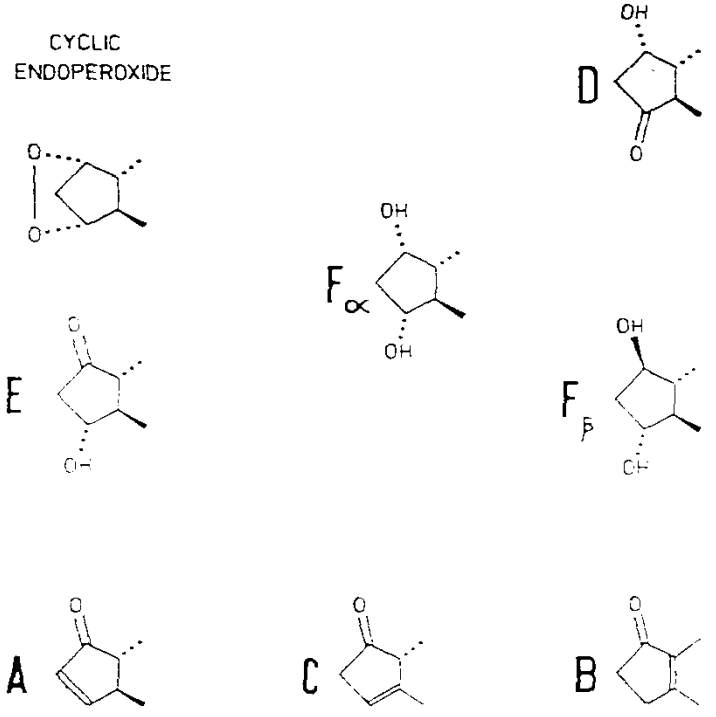

Figure 2: Comparison of the cyclopentane ring substituents in prostaglandins A to F.

carbon side chains; thus PGE_1 has only one double bond on its side chains, while PGE_2 has two double bonds, and PGE_3 has three double bonds. The subscript numeral also indicates to the fatty acid precursor from which the PG orginates. Figure 3, illustrates e.g.the 2 series orginating from arachidonic, while the 1 series is originating from the linolenic acid. Notably, the "two" series are the commonest PGs naturally existing due to the abundancy of arachidonic acid, while the " three" series are very rare in nature and may not even exist.

The subscript Latin letter (α or ß) which is added e.g. $PGF_{2\alpha}$, designates the configuration of C_9-Hydroxyl group whether on the same side as the carboxyl group (α) or on the opposite side(ß). Most naturally occuring PGs have α configuration, except PGF which can also exist in the ß configuration, and therefore α or ß subscripts are not omitted when PGF is concerned. PGs posses optical activity and the naturally ocurring ones are laevo-rotary (Bowman and Rand, 1980; Zurier, 1980; Caton, 1973).

II- BIOSYNTHESIS OF PROSTAGLANDINS

With the exception of seminal fluid, PGs are not stored, but they are synthesized de novo in response to diverse stimuli.

All mammalian tissue cells (except mature RBCs) are endowed with PG-synthetase enzyme, which enables them to form PGs, for example; kidneys, lungs, brains, spleen, uterus, heart, blood vessels, blood cells and platelets, and skeletal muscles have such an enzyme (Pong and Levine, 1977; Lands, 1979; McGiff, 1981). The newly synthesized PGs are released to enter the extracellular space, which is reflected as elevated levels in plasma, urine, and other biological fluids. After removal of the stimulus, PG levels rapidly subside as a result of metabolism, diffusion, and removal in blood, lymph, and urine (McGiff, 1981).

1- SUBSTRATE AVAILABILITY:

PGs are derived enzymatically from the essential fatty acid (EFA) precursors of the linoleic acid (LA) family. When ingested in diet (vegetable, oils, and meat), LA is modified enzymatically to dihomo-gama-linolenic acid (DGLA) which is the precursor of the "1" series PGs (fig.3). DGLA can be matabolised to yield arachidonic acid (AA) which is the precursor of the 2 series PGs. AA is also present in diets in daily intake but at low concentrations.