SUMMARY

Introduction :

The history of PGs goes back to 1930 when two American gynaecologist, observed that strips of human uterus relax or contract when exposed to fresh human semen. The term PGs was coined in 1935 by Von Euler in the belief that the newly discovered biologically active substances originated from the prostate gland.

PGs are a group of unsaturated fatty acid,derivatives which are formed by almost every cell studied, they are synthesized by a multiple enzyme complex "prostaglandin synthetase" which act on the substrate fatty acids, released from cell membrane phospholipids, by phospholipase, arachidonic acid is the most abundant of the three fatty acids that are precursors of prostaglandins, Once PGs are formed they are rapidly inactivated, both enzymatically and non enzymatically, and their metabolites appear in the plasma and urine, however, some of their metabolites do retain biological activities. Prostaglandins which may find their way to the general circulation are metabolized mainly in the lungs, liver and kidneys may play a role in this aspect.

Human platelets and RBCs constitute rather good models for the study of the cellular actions of PGs.

It was found that certain sites have higher affinity and specificity for PGs, known as PG receptors,through actions on these receptors, PGs can change the cellular content of cAMP and/or cGAMP and/or calcium ion concentration, still there is no definite mechanism for their actions.

Prostaglandins are not stored in cells, but are newly synthesized and released to act in the surroundings of the forming cells . They are formed in response to numerous and diverse stimuli.

Inhibitors of PGs either act through inhibition of their synthesis or through antagonism of their peripheral actions NSAIDs belong to the first group.

PGs are prepared either by direct extraction from tissues or through in vitro biosynthesis.

Three methods are identified for PG assay, none of them is satisfactory. Physiological ,pharmacological and pathological aspects (in the various body systems).

PGs are claimed to maintain foetal circulation and their inhibition, by indomethacin have been successfully used for the medical closure of patent ductus arteriosus, white their analogues were used to keep it opened in some cases where maintenance

of foetal circulation is essential for survival. In platelets the mainly formed PG is TXA_2 which is a potent platelet aggregator and vasoconstrictor , while PGI_2 is the main one formed by blood vessels and it exerts opposite effects to TXA_2 interaction between both PGI_2 and TXA_2 can play a major role in haemostasis and platelet homeostasis. When these two compounds are in balance, they act as regulators in the vascular system and perhaps in the repair of damaged arterial walls.

In the lungs, prostaglandins help in directing blood flow from hypoxic alveoli to the well aereated ones, thus ensuring adequate ventillation/perfusion ratio . They can keep the tone of airways by a balance between bronchodilatory and constrictor prostaglandins, and they prevent aggregation of platelets in the alveolar meshes. Constrictor prostaglandins ($PGF_{2\alpha}$, TXA_2) can mediate bronchial asthma, and their plasma and urinary metabolites are elevated in asthmatics; while dilator ones (PGE, PGI_2) can modulate it. Although the dilator prostaglandins are more potent than isoprenaline, their therapeutic use is limited because of the throat irritation and cough they produce when inhaled; such adverse effects are due to their stimulation of prostaglandin-irritant

receptors. A recent discovery of an analogue capable of stimulating prostaglandins-relaxant receptors may be promising.

Aspirin sensitivity in asthmatics may be due to inhibition of dilator PGs synthesis.

The capacity of the lungs to inactivate blood PGs exhibit the role of the lungs in protecting the organism against excess PGs.

Gut PGs exert a mucosal cytoprotective effect together with their ability to lower the gastric acid secretion. When this defensive mechanism is disturbed by the prolonged use of NSAIDs, ulceration may result . Inflammatory intestinal disorders e.g. ulcerative colitis is associated with excess production of PGs during acute attacks, sulphasalazine is effective in treatment as it yields a salicylate compound which inhibits PG formation. Excess PGs cause diarrhoea due to stimulation of gut motility and to an enteropooling effect inhibition of PGs successfully treat diarrhoea . A case reported with diarrhoea since birth with no abnormality detected, proved to be due to PG excess with an inborn error in the enzyme responsible for PG degradation.

Renal prostaglandins not only maintain the

renal circulation, but also they protect the organism against changes in blood pressure. By redirecting renal circulation from the absorptive medulla to the filtering cortex; postaglandins are diuretic and natriuretic, thus protecting against hypertension , therefore indomethacin can cause salt and water retention. Their interaction with the renin-angiotensin system can defend against hypotension by an opposite mechanism. Excess production of renal prostaglandins causes Bartter's syndrome which responds to the use of prostaglandin inhibitors. On the otherhand,prolonged inhibition of them like using NSAIDs for a long time, can cause medullary ischaemia with papillary necrosis "analegesic nephropathy". Moreover, diabetes insipidus may be due to the counteraction of the effects of ADH by PGE_2. Chlorpropamide is thought to be effective in this disorder by inhibiting prostaglandin synthesis.

PGs can act as modulators of neurotransmission, their levels have been found to be higher in patients with epilepsy, meningoencephalitis and hydrocephalus and lower in Schizophrenics. They may play a role in cerebro vascular accidents and Migraine. PGs may mediate the effect of endogenous pyrogens in causing fever.

PGs by changing Ca ion concentration inside muscle cells can cause muscle contraction or relaxation.

PGs can release, or could be released by most hormones including trophic ones thyroxin can inhibit PG degradation, therefore in hyperthyroidism,there are PG excess which may account for diarrhoea,worsening of bronchial asthma and increased temperature. PGs production were elevated in diabetics, the increased PG synthesis may be related to the vascular problem, that occur in diabetics. PGs tend to mobilize calcium from bones and cause hypercalcaemia, indomethacin can normalize the serum calcium.

PGs play a major role in inflammation. NSAIDs which are potent anti inflammatory agents, are weak inhibitors of the effects of Histamine, serotonin and kinins so the effect of these drugs as anti-inflammatory agent on belong mostly to PGs inhibition.

PGs are present in milk in large proportion than found in plasma, speculating that they may play a role in modulating neonatal physiology.

Essential fatty acids deficiency is known to lead to eczematoid skin lesions, suggesting that failure of PG formation may be one cause of eczema.

Local application of PGE_1 has been reported to clear plaques of psoriasis.

PGs by virtue of their ability to influence cellular cyclic nucleotides, appear to be participating in the regulation of cellular functions including those cells involved in the immune reactions. PG precursors tend to enhance, and PG synthesis inhibitors to inhibit lymphocyte function. On the other hand, there are evidences that PG precursors can inhibit lymphocyte transformation and exert an immunosuppression effect.

It in most patients with cancer, high levels of PGs and PG like material were detected suggesting that they may play a role in cancer. Hypercalcaemia found in many cancer patients may be related to increased PG production by the cancerous tissue failure of TXA_2 synthesis was proposed to the process of carcinogenesis and the uncontrolled growth of cancerous tissues.