

THE PROSTAGLANDINS: FROM THE LABORATORY TO THE CLINIC

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by

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The chemistry and biochemistry of the prostaglandins are now described in textbooks, and I have reviewed the early work several times (1-4). I will instead discuss the background of the early prostaglandin work here in Sweden and also some recent developments in the clinical fields that I have been associated with.

Now let me digress for a moment. My scientific work started with Dr Erik Jorpes in 1934 when I participated in his early heparin work. He is more responsible than anybody else for purifying heparin and introducing it as a drug into the clinic. At that time Professor Einar Hammarsten was Director of the Chemistry Department at the Karolinska, then one of the leading laboratories in the world also in the field of nucleic acids and of peptide hormones, i.e. secretin and cholecystokinin.

Dr Jorpes always maintained that it was too bad that nobody worked on lipids or steroids in Sweden. He financed a trip for me to England in 1938 where I spent a few months working on bile acids with Dr G.A.D. Haslewood at Hammersmith Postgraduate Medical School. The following year I got a fellowship from the British Council to work for a year at Dr Marrian's laboratory in Edinburgh. It was cancelled when the war broke out, but I was then lucky enough to get a Swedish American Fellowship and worked for a year and a half at Columbia University and at the Squibb Institute with Dr Oskar Wintersteiner on cholesterol autoxidation 1940-1942. After returning home I started working on the autoxidation of linoleic acid and identified the structure of the main reaction products. It was found that a conjugation of the double bonds took place and that oxygen was introduced as an hydroperoxide group at carbon atoms 9 or 13. I also found that the lipoxygenase enzyme of soy beans, just described by Dr Sumner, yielded the same products as the heavy metal catalyzed autoxidation. At that time I was working in Dr Hugo Theorell's laboratory, and we started to cooperate on the purification of the soy bean lipoxygenase enzyme.

My involvement with the prostaglandins started at the Meeting of the Physiological Society of Karolinska Institutet, October 19th, 1945 where I reported on my work on the oxidation of linoleic acid. Dr Hugo Theorell was chairman, Dr Yngve Zotterman secretary and Dr Ulf von Euler signed the minutes of the meeting.

After this meeting von Euler asked me if I might be interested to study the small amount of his lipid extracts of sheep vesicular glands that he had stored since before the war. I agreed, and we began a most stimulating and pleasant cooperation.

The first observation that there was some biologically active compounds in human semen had been done in the Department of Obstetrics and Gynecology at Columbia University in New York. In 1930 Kurzrok and Lieb with the technical cooperation of Dr Sara Ratner (5) reported that when they were doing artificial inseminations in women, they sometimes got violent contractions, sometimes relaxation, of the uterus.

An interesting coincidence is that I met Dr Kurzrok and worked at the same laboratory at Columbia University as Dr Sara Ratner for a year but never heard anything about prostaglandin.

In 1933 the British pharmacologist Goldblatt (6, 7) had reported that human semen contained a factor that reduced blood pressure and stimulated smooth muscle.

At about the same time Dr von Euler was making a thorough study of the occurrence of compound P in various organs, the peptide he had discovered a few years earlier. In semen and in extracts of "prostate" or vesicular glands of monkeys, sheep and goats there was a strong blood pressure decreasing factor that also stimulated smooth muscles. He showed that the factor was different from P, that it was lipid soluble and he gave it the name prostaglandin. Dr Theorell had shown that the activity behaved as an acid in his electrophoresis apparatus (8-10).

In the early work the rabbit intestinal strip test was used to follow the activity. We used mainly countercurrent extractions to purify von Euler's crude extract.

I had just brought home one of Dr Lyman Craig's stainless steel counter current extraction machines that proved ideal for working with these small amounts. We managed to purify the crude extract about 500 times. The most active fractions consisted of unsaturated hydroxy acids that were free of nitrogen (11).

The work was interrupted for a few years due to my appointment to the chair of physiological chemistry at the University of Lund in 1948.

A practically empty institution had to be rebuilt, reequipped and staffed, but it was a very fortunate time (1948) for the biomedical sciences in Sweden. The large buildup of resources for basic biomedical research at the Swedish Universities, initiated by the former Prime Minister Tage Erlander, had just started. The Swedish Medical Research Council had also just been started. An additional advantage during the following decade was that the National Institutes of Health (NIH) in the U.S.A. started their unique international programme of support of biomedical research.

We were fortunate to receive quite sizeable grants for our work in the field of steroid and bile acid metabolism from NIH for a number of years.

A group of able graduate students could then be trained in these fields-Bengt Borgström, Jan Sjövall, Sven Lindstedt, Henry Danielsson, Bengt Sa-

muleson and Rolf Blomstrand. They have all more or less directly contributed to the early prostaglandin development that was started up again in the fifties.

Collection of sheep glands was organized in Sweden and Norway. Using counter current fractionations and partition chromatography two crystalline compounds prostaglandin E₁ and F_{1α} (12-14) were isolated in small amounts in 1957.

The correct empirical formulas could be determined in cooperation with Wolfgang Kristen who had developed an ultramicro carbon-hydrogen determination in Dr Einar Stenhagen's laboratory in Uppsala. Together with the molecular weight, determined by Dr Ragnar Ryhage in his mass spectrometer, the formulas were found to be C₂₀H₃₄O₅ and C₂₀H₃₆O₅, respectively.

Collection of sheep glands was then expanded in Sweden, Norway, Iceland, Greenland and also in the U.S.A. through the Horniel Institute. These activities were generously supported by the Upjohn Co., U.S.A.

In 1958-1959 the whole research group moved from Lund to the Department of Chemistry at the Karolinska Institute in Stockholm. What really played a decisive role in the prostaglandin work was the mass spectrometer development that Dr Ragnar Ryhage was doing there. He had built the first

PROSTAGLANDINS E₁ AND F_{1α}
INFLUENCE OF WEAK ACID AND BASE

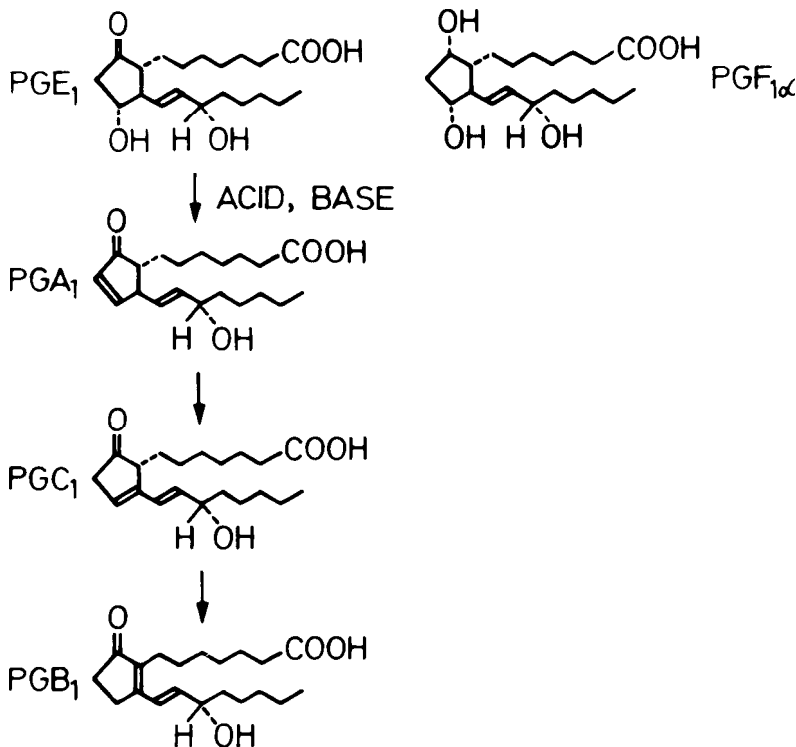


Figure 1. The influence of weak acid and base on PGE₁ and PGF_{1α}.

BIOSYNTHESIS OF PROSTAGLANDINS

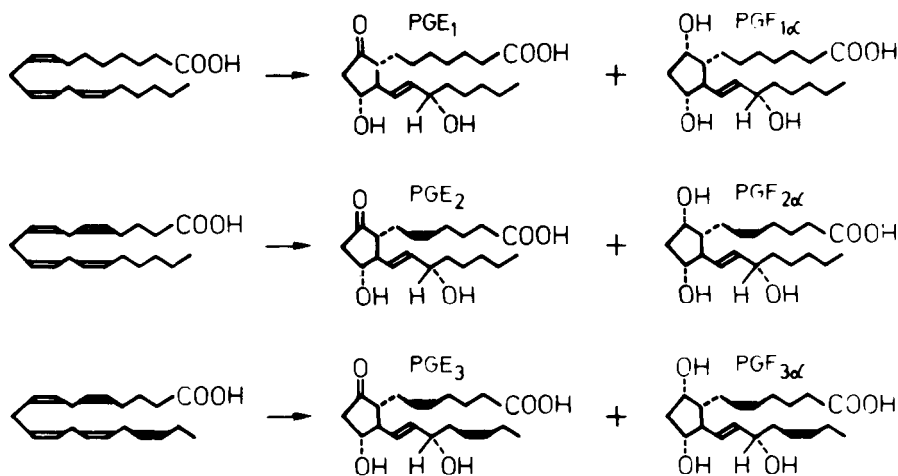


Figure 2. Biosynthesis of prostaglandins with homogenates of sheep vesicular glands.

functioning combination instrument of a gas chromatograph and a mass spectrometer. The structure of PGE₁ and F_{1α} was then deduced largely from mass spectrometric identification of the products formed by oxidative degradation of these prostaglandins and the compounds formed from PGE₁ by treatment with a weak acid or base indicated in Fig. 1. The structure was then confirmed and the stereochemistry determined by Dr Sixten Abrahamsson in Gothenburg on a derivative of PGF_{1α}. It took him about one year to do this using the technology of those days. Today it would take less than three weeks. The absolute configuration was finally settled (25,26).

By 1962 the six prostaglandins as listed in Fig. 2 had been isolated and their structures determined (15-24). It had also been found that these prostaglandins occur in many other tissues outside the male reproductive organs.

These 20-carbon prostaglandins have cis-double bonds located as in certain essential fatty acids, when counting from the carboxyl. This made us suspect that these naturally occurring acids might be precursors.

I then telephoned Dr David van Dorp at Unilevers Research Laboratories in Holland where these acids had been synthesized and isotopically labelled earlier. When I asked him if we could get some isotopically labelled C₂₀ acids, it turned out that he was also planning to start investigating if they were precursors, and he had just prepared isotopically labelled dihomogamma-linoleic acid for this purpose. He was most generous and sent us samples of the labelled acid. We started simultaneously incubating the labelled acids with homogenates of sheep glands and could inform each other after two days that indeed labelled prostaglandin E₁ and F_{1α} were produced in good yield. We published

our findings simultaneously in 1964. This work was then followed up with the labelled tetraenoic arachidonic acid and the pentaenoic acid shown in Fig. 2 which yielded prostaglandins of the 2 and 3 series, respectively (27-30). This discovery was also made independently at the Upjohn Co. using glands from bulls.

As the yields could be up to 70% these enzymatic methods were of great practical importance for getting material for further biochemical, physiological and pharmacological work.

We prepared several grammes of various prostaglandins whereas Unilever made considerably more, and the Upjohn Co. must have prepared hundreds of grammes.

In spite of the biosynthetic method the supply situation became critical around 1970 when prostaglandins were needed for clinical work before large scale total syntheses had been developed. An unexpected discovery was then made by Weinheimer and Spraggins (31) who had been studying the biochemistry of marine organisms in the Mexican Gulf. They found that up to one and one half percent of the dry weight of a *Gorgonia* coral consisted of 15 epiprostaglandin A₂ and related compounds. For several years the Upjohn Co. isolated these prostaglandins from corals which they transformed into the prostaglandins supplied for clinical trials. But from about 1973 the supplies have been prepared by total synthesis.

When the structure of the prostaglandins was published, many projects had been started on their total synthesis.

Dr E. J. Corey, who had collaborated with us in studies of the biosynthesis of bile acids with his stereospecifically labelled cholesterol, was the first to succeed. In a series of classical papers in 1968-69 (32-37) he described several elegant methods that still form the basis for most synthetic work in the prostaglandin field.

By that time many pharmaceutical industries had become interested in the field and large synthetic programmes to synthesize prostaglandin analogues were started. These synthetic efforts were in part guided by the knowledge of the metabolism of prostaglandins accumulated in Stockholm. More than 5000 prostaglandin analogues have now been prepared and tested in one way or another.

When the biosynthesis from the precursor acids was done with homogenates from lungs, it had been found that the prostaglandins formed were extensively further metabolized to inactive compounds (38-41) as indicated in Fig. 3, i.e. by saturation of the double bond between carbon 13 and 14 and dehydrogenation at C₁₅. These reactions are so effective *in vivo* that these prostaglandins are usually almost completely inactivated during one passage through the lungs. In later work *in vivo* it was found that these inactive compounds are further beta- and gamma-oxidized before excretion. A possible way to block the first reactions is to replace the C₁₅ hydrogen with a methyl group. The 15-methyl prostaglandins that were prepared by Bundy et al. at the Upjohn Co. (42) turned out to be very useful for clinical work and 15-methyl F_{2α} is now registered as a drug.

Some of the different analogues that have been studied in the clinic are listed

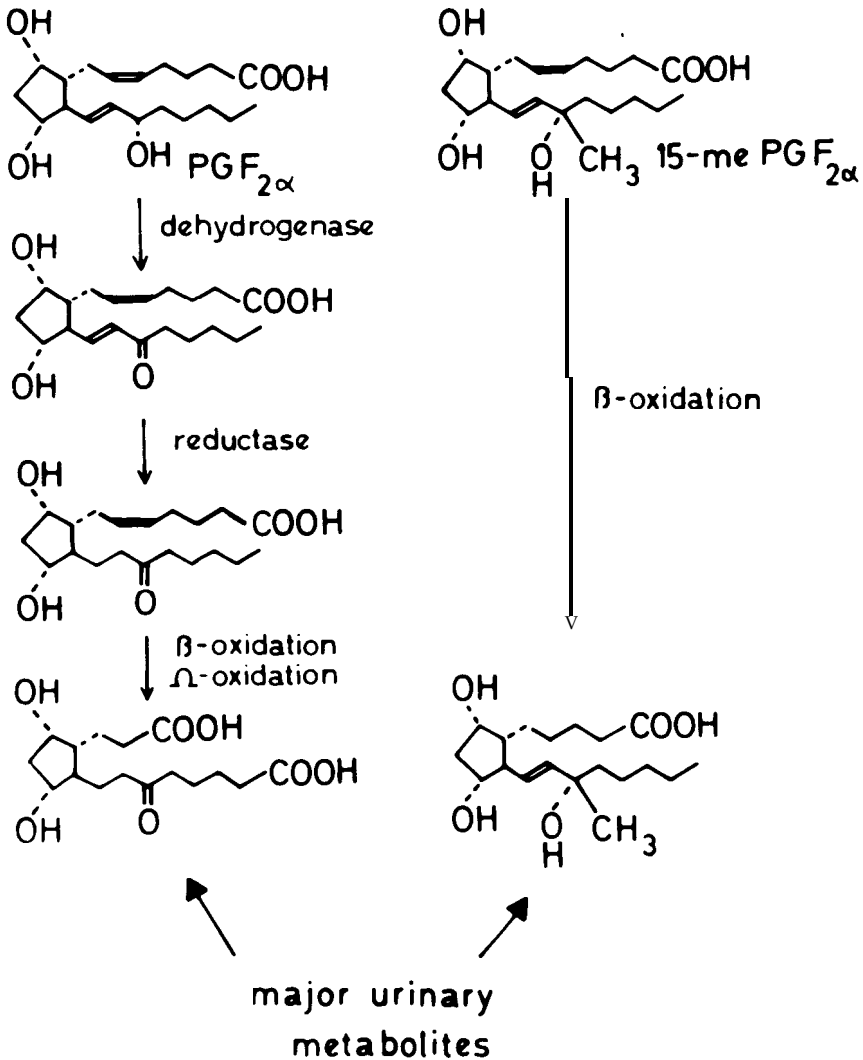


Figure 3. Main metabolic pathway of $\text{PGF}_{2\alpha}$ and its inhibition by the methyl group at C-15.

in Fig. 4. All are prepared by the Upjohn Co. unless indicated. These efforts to get compounds with longer lasting or more specific actions are continuing.

In the early sixties we had some difficulty trying to convince our colleagues to study the properties of the prostaglandins in their various pharmacological and physiological systems. This changed especially after early studies done in cooperation with Drs Dan Steinberg, Martha Vaughan and Jack Orloff at the National Institutes of Health (43-47). They were working with rat adipose tissue that releases glycerol and fatty acids due to increased lipolysis when stimulated with epinephrine, norepinephrine, glucagon or ACTH. It was found that PGE_1 and PGE_2 strongly inhibited the effects of all these compounds. PGE_1 and PGE_2 were also found to counteract both the lipolysis and the blood

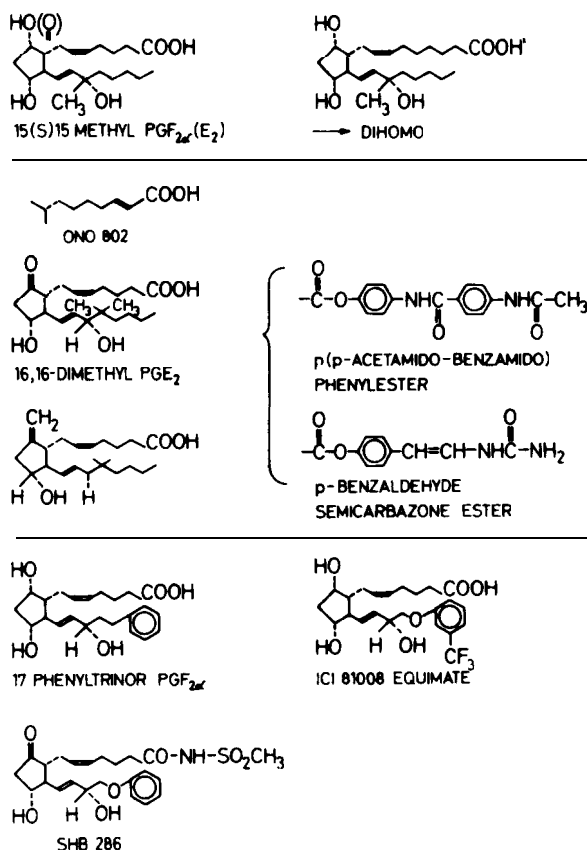


Figure 4. Some prostaglandin analogues that have been studied in clinical trials.

pressure effect caused by epinephrin e *in vivo*. It was later found that these effects were mediated by a decrease in the level of cyclic AMP in the fat cells. In this case the level was decreased. In most other cell types the E prostaglandins raise the level of cAMP. In some cases the F prostaglandins have been shown to influence the level of cyclic GMP. I am not going further into this field, but these findings explain why various prostaglandins can influence the metabolism of so many different cell types. A comprehensive summary of the early studies of the biological effects of the prostaglandin was published in 1968 (48).

It turned out that there were not only large differences between the effects of different prostaglandins and their analogues but also between different animal species. Obviously one had to turn to clinical studies in order to explore the physiological role and therapeutic potential of these compounds.

The first study on the cardiovascular effects of the pure prostaglandins in humans was done at the Karolinska (49, 50). In humans PGE₁ caused a fall in blood pressure and an increase in heart rate. My colleagues Drs Lars A. Carlson, Bengt Pernow and Lennart Kaijser and their collaborators have done much of the early, fundamental work on the effects of various analogues on the human cardiovascular system (51-54).

Dr Carlson and his collaborators demonstrated that 1/100 of a milligram of

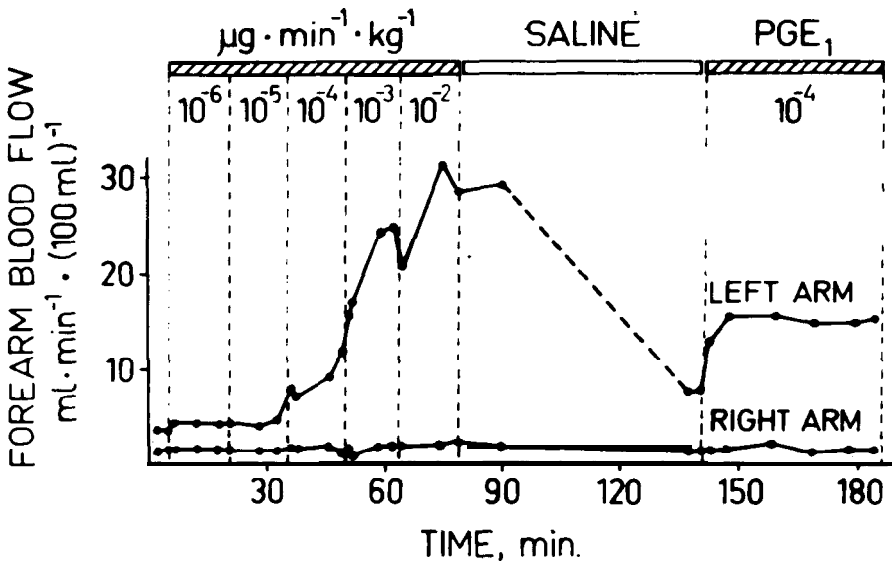


Figure 5. The effect on forearm blood flow of continuous intraarterial infusion of PGE₁ into left brachial artery.

PGE₁ can increase the blood flow through an arm tenfold if it is given intraarterially (Fig 5). No change was seen in the other arm as the compound is inactivated during the passage through the lungs (55). Together with Dr Anders Olsson he has developed this observation into a therapy for peripheral vascular diseases; in some cases this therapy has a dramatic effect.

Another therapeutic utility relates to the patency of *Ductus arteriosus*. It normally closes soon after birth. In certain cases of congenital malformations the E prostaglandins have found clinical use to keep the ductus open for a few days so that corrective surgery can be performed a few days later with less danger to the newborn baby.

On the other hand, the closure of a ductus that remains open can be supported by administration of a cyclooxygenase inhibitor like aspirin or indomethacin etc. that inhibits the local prostaglandin synthesis.

I will now turn to the effects of prostaglandins on the gastrointestinal tract, a field in which Dr Robert of the Upjohn Co. has been very active. In animal experiments he found that the gastric secretion could be inhibited by oral administration or injections of prostaglandins of the E-type. The methyl analogues 15(S) 15-methyl PGE₂ and 16,16-dimethyl PGE₂ were many times more active than PGE₂ itself (58). Early clinical studies were done here in Stockholm by the late Drs Sven Andersson and B. Nylander. They found that an oral dose of only 80 microgrammes of 16,16-dimethyl PGE practically blocked the pentagastrin stimulated gastric secretion in humans for several hours (Fig. 6). This work has been continued and expanded upon by Dr Catja Johansson and her collaborators. Extensive clinical trials in many countries have been conducted that have demonstrated a healing effect on ulcers with several analogues. For a recent summary see (58).

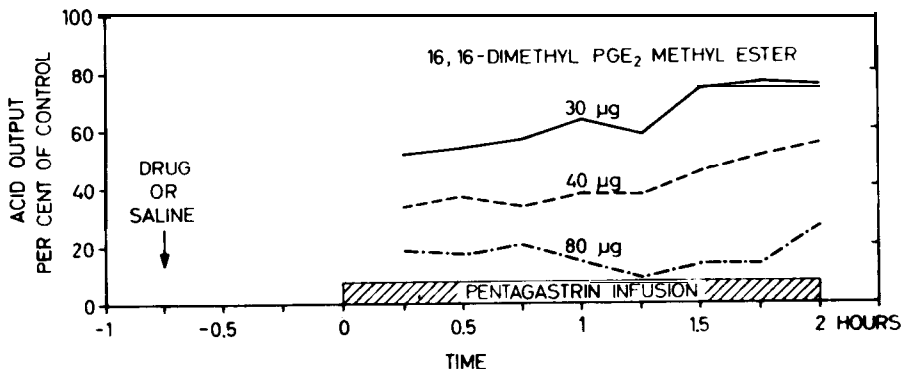


Figure 6. The effect of 16,16-dimethyl prostaglandin E₂ on gastric secretion.

Another important observation that Dr Robert made was a phenomenon that he called "cytoprotection". If large doses of indomethacin or aspirin are administered to rats or if you give boiling water, strong acid or base orally to anesthetized rats, extensive erosions and/or bleeding of the gastric mucosa occurs and the animals usually die in a few days. But if less than a microgramme of 16,16-dimethyl PGE₂ is administered orally 30 minutes beforehand, the mucosa is protected. An interesting observation by Robert et al. (59) is also that mild irritants like dilute ethanol can effect a certain protection presumably by stimulating the mucosal cells to an increased biosynthesis of prostaglandins. Cytoprotection can be observed at doses and with prostaglandins that do not inhibit acid secretion. Some prostaglandins stimulate secretion of mucus and bicarbonate. The mechanism of cytoprotection is not clear but it is certainly a reality (58). The effect is not limited to the gastrointestinal mucosa. Liver and kidney cells can also be protected to some extent from necrosis caused by carbontetrachloride, etc. by administration of 16,16-dimethyl PGE₂ (60).

It was logical at this point to look into the effect of cytoprotective prostaglandins on some clinical side effects of indomethacin and aspirin. Normally there is an invisible bleeding of a fraction of one ml of blood from the gut per day. The usual therapeutic dose of indomethacin increases this amount to 3 to 5 ml and in a few cases causes serious bleedings. It was demonstrated here at the Karolinska for the first time that only a third of a milligram of PGE₂ or 40 microgrammes \times 3 of 15(R) 15-methyl PGE₂ (61, 62) completely protected the patient from this bleeding caused by indomethacin (Fig. 7). It is still too early to evaluate the therapeutic utility of the administration of prostaglandins to reduce the side effects of these drugs (NSAID).

The last aspects that I will discuss are related to fertility and the use of prostaglandins in obstetrics and gynecology. That is where the prostaglandins were discovered, and that is where they have found their greatest utility so far.

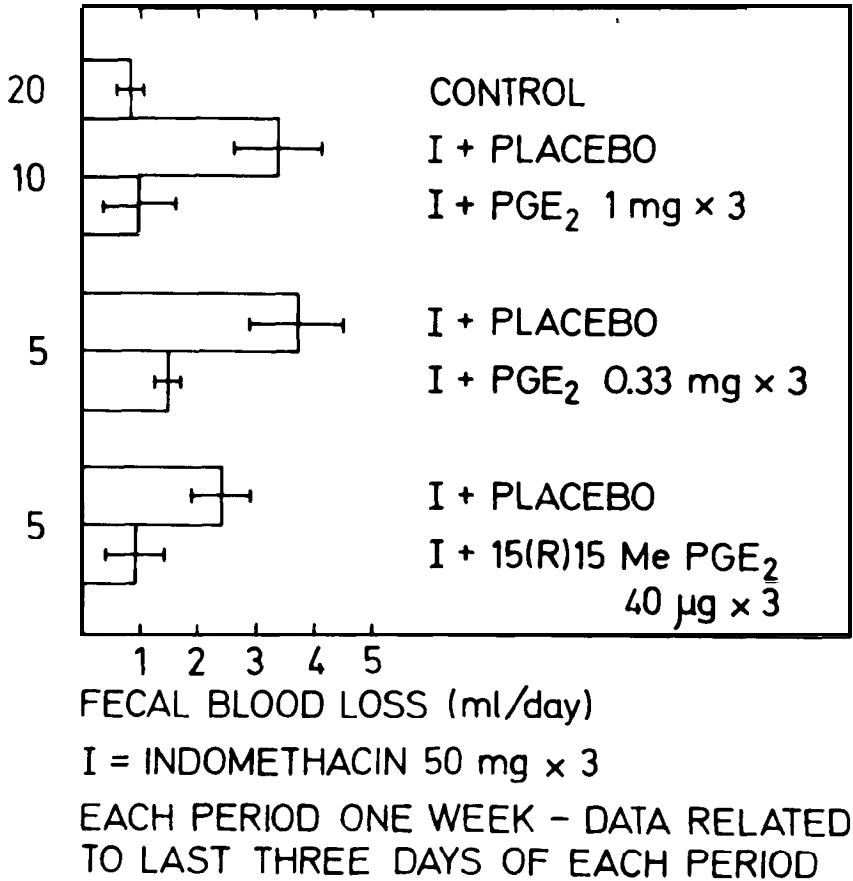


Figure 7. The effect of prostaglandins on the fecal blood loss during indomethacin administration.

Dr Marc Bygdeman had just started his thesis work with Dr von Euler when the pure prostaglandins became available. He studied the effects of the different prostaglandins first *in vitro* and then *in vivo* in Dr Ulf Borell's Department at the Karolinska together with Dr Nils Wiquist. They first demonstrated clinically that PGE₁ causes uterine contractions when injected in small amounts. This of course led to the expectation that administration of prostaglandins might initiate labor or cause pregnancy interruption (63-65).

Dr Sultan Karim was the first to report on the clinical use of prostaglandins to initiate labor.

The first therapeutic abortion with PGF_{2α} was done in May 1969 at the Karolinska Institute. During the remainder of the year the scientists at the Karolinska and also Drs Karim and Filshie in Uganda conducted further studies with PGF_{2α} and PGE₂. The results of both groups were published in the same number of *Lancet* in January 1970 (66, 67).

An intense activity then started all around the world exploring these findings with normal prostaglandins and later with some of the analogues as shown in Fig. 4.

APPROXIMATE DOSES FOR PREGNANCY INTERRUPTION


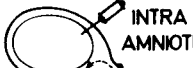




	PGF _{2α}	PGE ₂	15(S) 15 Me F _{2α}	16,16 diMe E ₂
INTRA VENOUS 	~ 100 mg (50-100 µg/min)	~ 5 mg 5 µg/min	~ 5 mg 5 µg/min	~ 0.5 mg 0.5 µg/min
INTRA AMNIOTIC 	40-50 mg (1×)	5-10 mg (1×)	2.5 mg (1×)	
EXTRA AMNIOTIC 	~ 5 mg (~ 9×0.75 mg)	1-2 mg (6×)	1 mg (1×)	
I. VAGINAL SUPPOSITORIES 	[250 mg (5 × 50 mg)]	60-80 mg (3-4 × 20 mg)	~3 mg (Me-ester) (1 × 3 mg)	~4 mg (4 × 1 mg)
I. MUSCULAR 	—	—	2 mg (6 × 0.3)	
ORAL 	—	—	—	0.2-0.6 mg (60% Success)

Figure 8. Summary of early clinical trials indicating approximate doses for interruption of pregnancy.

The early clinical data that were obtained in Stockholm are summarized in Fig. 8 (66-73).

The two natural prostaglandins PGE₂ and F_{2α} were first studied extensively. When they were administered i. v. they caused very pronounced side effect. When administered intraamniotically or extraamniotically the side effects were tolerable.

The 15(S)15-methyl PGF_{2α} that was supplied by the Upjohn Co., was then studied and found to be much more active and giving much less side effects. It could also be injected i. m., and we developed vaginal suppositories containing the methyl ester. It is now a registered drug in many countries.

16,16-dimethyl PGE₂ was even more active-sometimes also very effective after oral administration of less than a milligramme. It caused, however, more side effects and furthermore had stability problems. Recently an analogue of 16,16-dimethyl PGE₂ in which the carbonyl group at C9 has been replaced by a methylene group is being extensively studied as it combines high activity with stability and very low side effects (74).

At that time an important development was initiated by SIDA (the Swedish International Development Authority). In the sixties they had become heavily involved in supporting family planning in many developing countries. However, they found that the methods available left much to be desired and therefore were considering how best to stimulate and support research and development in the field.

The Director, Mr Ernst Michanek and Mr Carl Wahren had developed

advanced plans to start an international research foundation located here at the Karolinska for this purpose. However, for various reasons, it was decided to make a feasibility study of an alternative arrangement together with the Ford Foundation and WHO, in which I had the honor to participate. This resulted in the creation of WHO's "Special programme" for research on human reproduction in 1971-72. The work should be focused on the needs of developing countries. The voluntary contributions to the programme soon exceeded ten million US dollars annually of which more than half were provided from Swedish sources during the seventies.

One of the "Task Forces" of the programme was devoted to exploring the potential of the prostaglandins to interrupt pregnancy. During the first live years I had the stimulating assignment as chairman of this group of outstanding experts. The exploratory work done at the Karolinska and by Dr Karim's group formed the basis for large international coordinated clinical trials. Figure 9 indicates the locations of the cooperating clinics and Fig. 10 the number of cases completed. The Task Force has continued its activities under the chairmanship of Dr Bygdeman.

The most important new development has been the interruption of pregnancy during the "postconceptional" period, i.e. the first three weeks after a missed menstrual period.

I have a very vivid memory of a late evening in Bombay when Dr Borell, Dr Bygdeman and myself were compiling results of abortions during different weeks of pregnancy and found a success rate of practically 100 per cent complete abortions during this period (Fig. 11). This observation has been studied extensively, and Dr Bygdeman et al. has just completed a successful trial with a hundred cases in Stockholm in which the patients even administered the drug themselves in their home. This method obviously has a very great potential especially in developing countries.

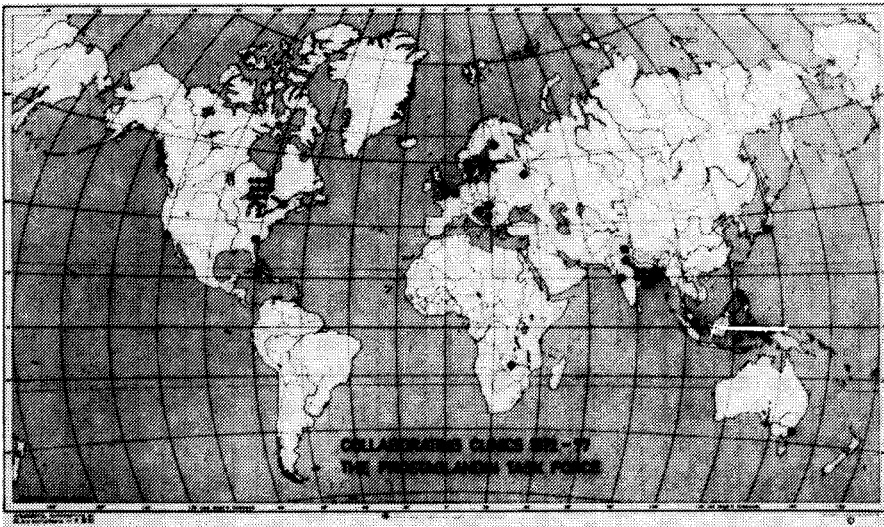


Figure 9. Participating clinics in coordinated trials of the WHO Prostaglandin Task Force.

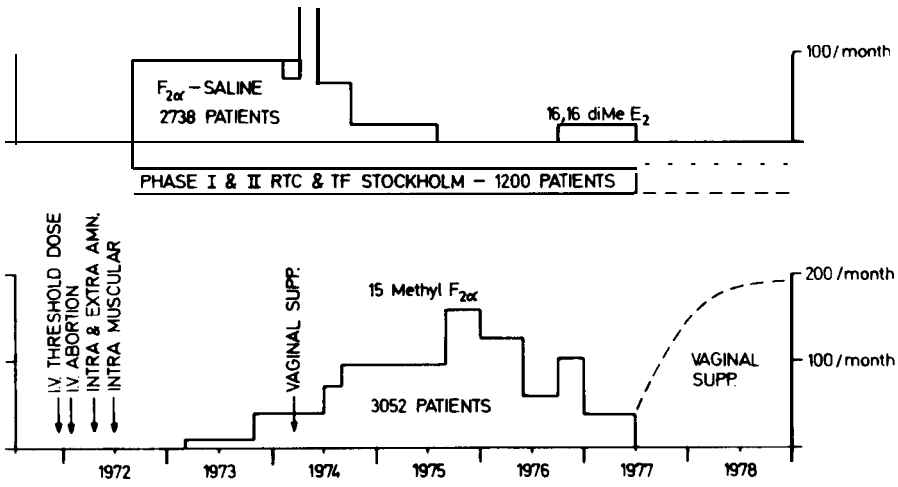


Figure 10. Number of patients participating in coordinated trials of the WHO Prostaglandin Task Force.

USE OF PROSTAGLANDINS FOR INTERRUPTION OF PREGNANCY

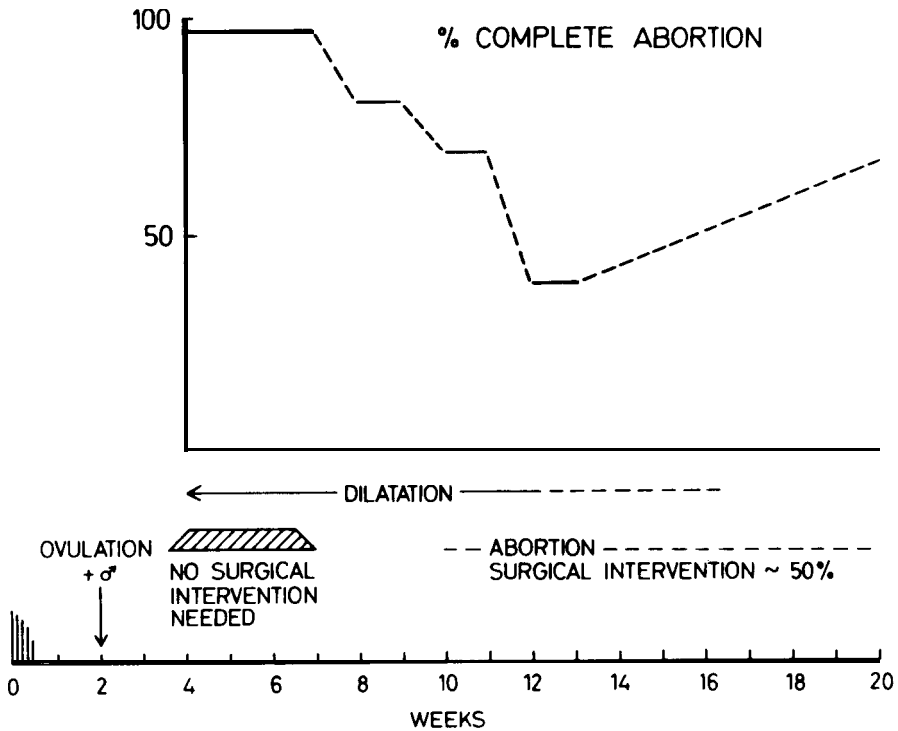


Figure 11. Per cent of "complete" abortions after interruption with prostaglandins during different weeks of pregnancy.

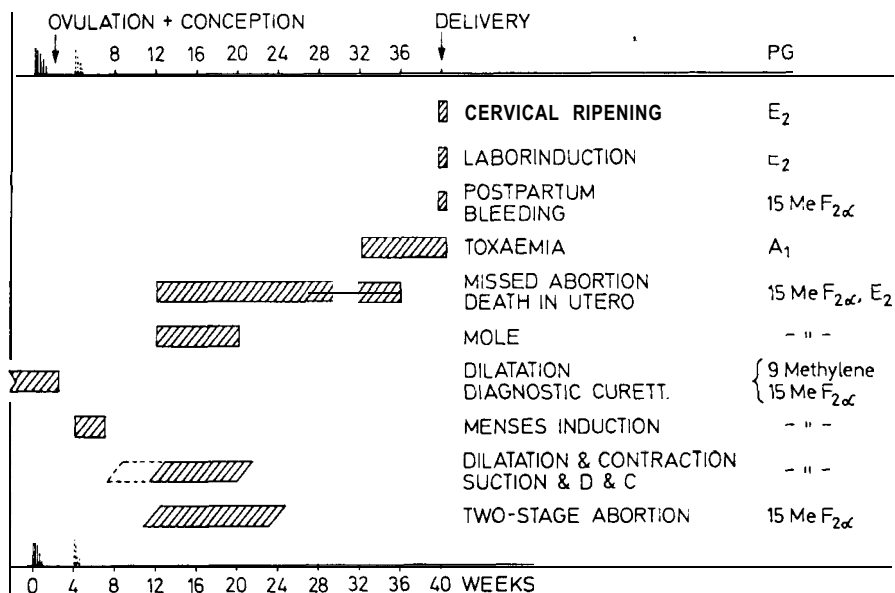


Figure 12. Summary of therapeutic utility of prostaglandins in human fertility

The therapeutic use of prostaglandins is, however, not limited to interruption of pregnancy. It is being used for labor induction, treatment of serious bleeding after delivery and dilatation for diagnostic curettage. Promising results have been reported of treating eclampsia with PGA_1 , by Dr M. Topozada in Alexandria.

A summary of the use of prostaglandins in the fertility area is given in Fig. 12.

Prostaglandins have also found extensive use in animal husbandry especially for "synchronization" of herds of cattle, i.e. after injection of cows with 25 mg of $PGF_{2\alpha}$ at an appropriate time, their cycles are interrupted and the whole herd can be inseminated three days later.

My presentation has of necessity been very short and sketchy and will be complemented by my colleagues.

The prostaglandin precursors and the enzymic systems appear to be present in practically all nucleated animal cells. They can biosynthesize characteristic mixtures depending on cell type and conditions on appropriate stimulation. As the highest concentration is found in the lowest animal species one can speculate that the ease of autoxidation of the precursor acids - a reaction that has even been reported to produce prostaglandins in minute amounts (75) - has led to their utilization in metabolism early on in development and for many different functions.

They are apparently mainly playing a role as local regulators even if $PGF_{2\alpha}$ functions as a classical hormone in sheep, where it is produced in the uterus at the end of the cycle and transported in the blood to the ovary where it causes luteolysis.

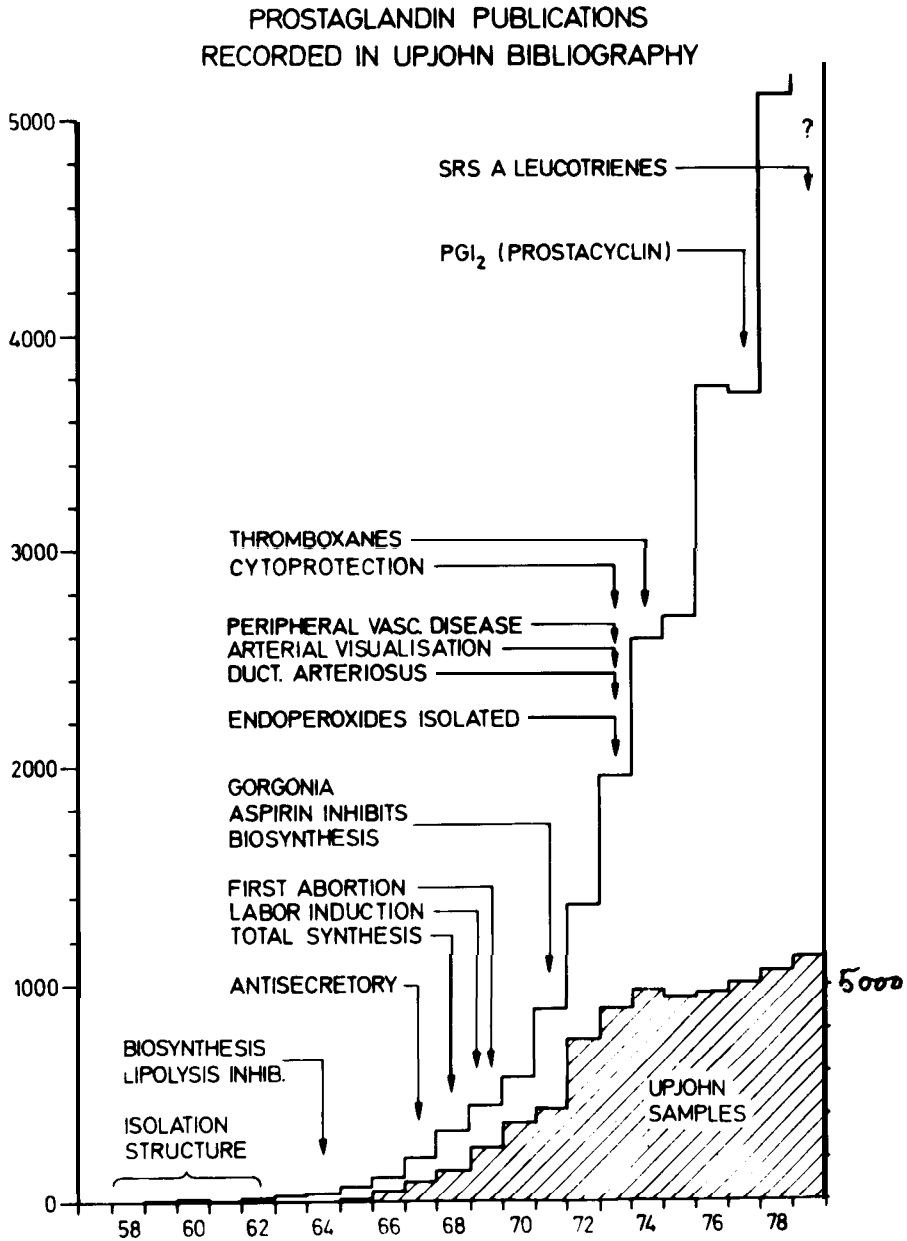


Figure 13. Annual publications related to prostaglandins in relation to the scientific development of the field. Free samples of prostaglandins distributed by the Upjohn Co., Kalamazoo.

The complex pattern of the arachidonic acid metabolism makes studies of the roles of prostaglandins in the complex regulatory mechanisms in organs like the kidney, lung etc. a difficult and challenging task.

Figure 13 illustrates how the field has developed from the early publications on the isolation, structure and biosynthesis to the present level of more than live thousand papers annually.

'How did all these scientists get their prostaglandins?' It is illustrated in Fig. 13. The Upjohn Company has sent out something like 75000 free samples during this period, and you can see that there is a correlation between the number of publications and samples up to about 1970. At that point the prostaglandin containing coral was found in the Mexican Gulf. A number of pharmaceutical industries collected corals, started synthetic programmes and then also supplied samples to scientists.

At this moment it is appropriate to point out that the whole prostaglandin field had been very much slower in developing without the outstanding research and development work and generous supply policy that was initiated and organized at the Upjohn Co. by Dr David Weisblat.

The prostaglandin story again illustrates the importance of interaction between the pharmaceutical industry and the academic biomedical scientists. In this case the special programme for human reproduction of the World Health Organization has also greatly contributed to the speed of development and to the buildup of research and development capabilities in this field in developing countries.

REFERENCES

1. Bergström S. The prostaglandins. *Recent Progr. Hormone Res.* 22: 153-175, 1966.
2. Bergström S. Prostaglandins: Members of a new hormonal system. *Science (N.Y.)* 157: 382-391, 1967.
3. Bergström S. Isolation, structure and action of the prostaglandins. In: *Prostaglandins, Proc. 2nd Nobel Symp., Stockholm, June 1966*, ed. by S. Bergström and B. Samuelsson, pp. 21-30, Almqvist and Wiksell, Stockholm; Interscience, New York, 1967.
4. Bergström S., and Samuelsson B. Prostaglandins. *Annu. Rev. Biochem.* 34: 101-108, 1965.
5. Kurzrok R., and Lieb C.C. Biochemical studies of human semen. II. The action of semen on the human uterus. *Proc. Soc. Exp. Biol. Med.* 28: 268-272, 1930.
6. Goldblatt M.W. A depressor substance in seminal fluid. *J. Soc. Chem. Ind. (London)* 52: 1056-1057, 1933.
7. Goldblatt M.W. Properties of human seminal plasma. *J. Physiol. (London)* 81: 208-218, 1935.
8. Euler U.S. von. Zur Kenntnis der pharmakologischen Wirkungen von Nativsekreten und Extracten männlicher accessorischer Geschlechtsdrüsen. *Arch. Exp. Pathol. Pharmacol.* 175: 78-81, 1934.
9. Euler U.S. von A depressor substance in the vesicular gland. *J. Physiol. (London)* 84: 21P, 1935.
10. Euler U.S. von. On the specific vasodilating and plain muscle stimulating substances from accessory genital glands in man and certain animals (prostaglandin and vesiglandin). *J. Physiol. (London)* 88: 213-234, 1937.
11. Bergström S. Prostaglandinets kemi. *Nord. Med.* 42: 1465-1466, 1949.
12. Bergström S., and Sjövall J. The isolation of prostaglandin. *Acta Chem. Scand.* 11: 1086, 1957.
13. Bergström S., and Sjövall J. The isolation of prostaglandin F from sheep prostate glands. *Acta Chem. Scand.* 14: 1693-1700, 1960.
14. Bergström S., and Sjövall J. The isolation of prostaglandin E from sheep prostate glands. *Acta Chem. Scand.* 14: 1701-1705, 1960.
15. Bergström S., Dressler F., Krabisch L., Ryhage R., and Sjövall J. The isolation and structure of a smooth muscle stimulating factor in normal sheep and pig lungs. *Arkiv Kern.* 20: 63-66, 1962.
16. Bergström S., Dressler F., Ryhage R., Samuelsson B., and Sjövall J. The isolation of two further prostaglandins from sheep prostate glands. *Arkiv Kern.* 19: 563-567, 1962.
17. Bergström S., Krabisch L., Samuelsson B., and Sjövall J. Preparation of prostaglandin F from prostaglandin E. *Acta Chem. Scand.* 16: 969-974, 1962.
18. Bergström S., Krabisch L., and Sjövall J. Smooth muscle stimulating factors in ram semen. *Acta Chem. Scand.* 14: 1706-1710, 1960.
19. Bergström S., Ryhage R., Samuelsson B., and Sjövall J. The structure of prostaglandin E₁ and F₁. *Acta Chem. Scand.* 16: 501-502, 1962.
20. Bergström S., Ryhage R., Samuelsson B., and Sjövall J. Degradation studies on prostaglandins. *Acta Chem. Scand.* 17: 2271-2280, 1963.
21. Bergström S., Ryhage R., Samuelsson B., and Sjövall J. The structures of prostaglandin E₁ and F₁. *J. Biol. Chem.* 238: 3555-3564, 1963.
22. Bergström S., and Samuelsson B. Isolation of prostaglandin E₁ from human seminal plasma. *J. Biol. Chem.* 237: PC3005-PC3006, 1962.
23. Samuelsson B. The structure of prostaglandin E₁. *J. Amer. Chem. Soc.* 85: 34P, 1963.
24. Samuelsson B. Isolation and identification of prostaglandins from human seminal plasma. *J. Biol. Chem.* 238: 3229-3234, 1963.
25. Abrahamsson S., Bergström S., and Samuelsson B. The absolute configuration of prostaglandin F₂. *Proc. Chem. Soc.* 332, 1962.
26. Nugteren D.H., and Dorp D.A. van, Bergström S., Hamberg M., and Samuelsson B. Absolute configuration of the prostaglandins. *Nature (London)* 212: 38-39, 1966.
27. Bergström S., Danielsson H., Klenberg D., and Samuelsson B. The enzymatic conversion of essential fatty acids into prostaglandins. *J. Biol. Chem.* 239: PC4006-PC4008, 1964.

28. Bergström S., Danielsson H., and Samuelsson B. The enzymatic formation of prostaglandin E₁ from arachidonic acid. *Biochim. Biophys. Acta* 90: 207-210, 1961.
29. Dorp D.A. van, Beerthuis R.K., Nugteren D.H. and Vonkeman H. The biosynthesis of prostaglandins. *Biochim. Biophys. Acta* 90: 204-207, 1964.
30. Dorp D.A. van, Beerthuis R.K., Nugteren D.H., and Vonkeman H. Enzymatic conversion of all-cis-polyunsaturated fatty acids into prostaglandins. *Nature (London)* 203: 839-941, 1964.
31. Weinheimer A.J., and Spraggins R.L. The occurrence of two new prostaglandin derivatives in the gorgonian *Plexora Homomalla*. *Chemistry of Coelentrates. XV. Tetrahedron Letters* 5185-5188, 1969.
32. Corey E.J., Vlattas I., Andersen N.H., and Harding K. A new total synthesis of prostaglandins of the E₁ and F₁ series including 11-epiprostaglandins. *J. Amer. Chem. Soc.* 90: 3247, 1968.
33. Corey E.J., Andersen N.H., Carlson R.M., Paust J., Vedejs E., Vlattas I., and Winter R.E.K. Total synthesis of prostaglandins. Synthesis of the pure dl-E₁, -F_{1α}, -F_{1β}, -A₁ and -B₁ hormones. *J. Amer. Chem. Soc.* 90: 3245-3247, 1968.
34. Corey E.J., Weinshenker N.M., Shaaf, T.K., and Huber W. Stereo-controlled synthesis of prostaglandins F_{1α} and E₁ (dl). *J. Amer. Chem. Soc.* 91: 5675-5677, 1969.
35. Corey E.J., Vlattas I., and Harding K. Total synthesis of natural (levo) and enantiometric (dextro) forms of prostaglandin E₁. *J. Amer. Chem. Soc.* 91: 535-536, 1969.
36. Corey E.J., Arnold Z., and Hutton J. Total synthesis of prostaglandins E₁ and F_{2α} (dl) via a tricarbo-cyclic intermediate. *Tetrahedron Letters* 307-310, 1970.
37. Corey E.J., Noyori R., and Schaaf T.K. Total synthesis of prostaglandins F_{1α}, E₁, F_{2α}, and E₂ (natural forms) from a common synthetic intermediate. *J. Amer. Chem. Soc.* 92: 2586-2587, 1970.
38. Änggård E., Green K., Samuelsson B. Synthesis of tritium-labeled prostaglandin E₁ and studies on its metabolism in guinea pig lung. *J. Biol. Chem.* 240: 1932-1940, 1965.
39. Änggård E., and Samuelsson B. Biosynthesis of prostaglandins from arachidonic acid in guinea pig lung. *J. Biol. Chem.* 240: 3518-3521, 1965.
40. Änggård E., and Samuelsson B. The metabolism of prostaglandins in lung tissue. In: *Prostaglandins, Proc. 2nd Nobel Symp., Stockholm, June 1966*, ed. by S. Bergström and B. Samuelsson, pp. 97-106, Almquist and Wiksell, Stockholm; Interscience, New York, 1967.
41. Änggård E., and Samuelsson B. Metabolism of prostaglandin E₁ in guinea pig lung: The structure of two metabolites. *J. Biol. Chem.* 239: 4097-4102, 1964.
42. Bundy G.L., Lincoln F.H., Nelson N.A., Pike J.E., and Schneider W.P. Novel prostaglandin syntheses. *Annal. N.Y. Acad. Sci., Prostaglandins* 180: 76-79, 1971.
43. Steinberg D., Vaughan M., Nestel P., and Bergström S. Effects of prostaglandin E₁ opposing those of catecholamines on blood pressure and on triglyceride breakdown in adipose tissue. *Biochem. Pharmacol.* 12: 764-766, 1963.
44. Steinberg D., Vaughan M., Nestel P.J., Strand O., and Bergström S. Effects of the prostaglandins on hormone-induced mobilization of free fatty acids. *J. Clin. Invest.* 43: 1533-1540, 1964.
45. Orloff J., Handler J.S., and Bergström S. Effect of prostaglandin (PGE₁) on the permeability response of the toad bladder to vasopressin, theophylline and adenosine 3', 5' monophosphate. *Nature (London)* 205: 397-398, 1965.
46. Orloff J., and Grantham J. The effect of prostaglandin (PGE₁) on the permeability response of rabbit collecting tubules to vasopressin. In: *Prostaglandins, Proc. 2nd Nobel Symp., Stockholm, June 1966*, ed. by S. Bergström and B. Samuelsson, pp. 143-146, Almquist and Wiksell, Stockholm; Interscience, New York, 1967.
47. Orloff J., and Handler J. The role of adenosine 3,5-phosphate in the action of antidiuretic hormone. *Amer. J. Med.* 47: 757-768, 1967.
48. Bergström S., Carlson L.A., and Weeks J.R. The prostaglandins: A family of biologically active lipids. *Pharmacol. Rev.* 20: 1-48, 1968.
49. Bergström S., Dunér H., von Euler U.S., Pernow B., and Sjövall J. Observations on the effects of infusion of prostaglandin E₁ in man. *Acta Physiol. Scand.* 45: 145-151, 1959.
50. Bergström S., Eliasson R., von Euler U.S., and Sjövall J. Some biological effects of two crystalline prostaglandin factors. *Acta Physiol. Scand.* 45: 133-144, 1959.

51. Carlson L.A. Metabolic and cardio-vascular effects in vivo of prostaglandins. In: Prostaglandins, Proc. 2nd Nobel Symp., Stockholm, June 1966, ed. by S. Bergström and B. Samuelsson, pp. 123-132, Almquist and Wiksell, Stockholm; Interscience, New York, 1967.
52. Carlson L.A., Ekelund L.-G. and Or6 L. Clinical and metabolic effects of different doses of prostaglandin E₁ in man. *Acta Med. Scand.* 183: 423-430, 1968.
53. Carlson L.A., and Hallberg D. Basal lipolysis and effects of noradrenaline and prostaglandin E₁ on lipolysis in human subcutaneous and omental adipose tissue. *J. Lab. Clin. Med.* 71: 368-377, 1968.
54. Carlson L.A., Irion E., and Or6 L. Effect of infusion of prostaglandin E₁ on the aggregation of blood platelets in man. *Life Sci* 7: 85-90, 1968.
55. Bevegård S., and Or6 L. Effect of prostaglandin E₁ on forearm blood flow. *Scand. J. clin. Lab. Invest.* 23: 347-353, 1969.
56. Robert A. The inhibitory effects of prostaglandins on gastric secretion. *Progress in Gastroenterol.* Vol. III. G.B.J. Glass (ed.). Grune and Stratton, New York 1977, 777-801.
57. Nylander B., Andersson S. Gastric secretory inhibition induced by three methyl analogs of prostaglandin E₂ administered intragastrically to man. *Scand. J. Gastroent.* 9: 751-758, 1974.
58. Johansson C., and Bergström S. Prostaglandins and protection of the gastroduodenal mucosa. *Scand. J. Gastroenterol. Suppl. nr. 77:* 21-46, 1982.
59. Robert A., Lancaster C., Hanchar A.J., and Nezamis J.E. Mild irritants prevent gastric necrosis through prostaglandin formation: histological study. *Gastroenterology* 74: 1086, 1978.
60. Ruwart M.J., Rush B.D., Friedle N.M., Piper R.C., Kolaja G.J. Protective effects of 16,16 dimethyl PGE₂ on the liver and kidney. *Prostaglandins* 21: 97-102, 1981.
61. Johansson C., Kollberg B., Nordemar R., Samuelsson K., and Bergström S. Protective treatment with prostaglandin E₂ in the gastrointestinal tract during indomethacin treatment of rheumatic patients. *Gastroenterology* 76: 479-483, 1980.
62. Cohen M.M., Cheung G., and Lyster D.M. Prevention of aspirin-induced faecal blood loss by prostaglandin E₂. *Gut* 21: 602-606, 1980.
63. Bygdeman M., and Eliasson R. A comparative study on the effect of different prostaglandin compounds on the motility of the isolated human myometrium. *Medicina experimentalis* 9: 409-415, 1963.
64. Bygdeman M. The effect of different prostaglandins on human myometrium in vitro. *Acta Physiol. Scand.*, 63, Suppl. 242, 1 – 78, 1964.
65. Bygdeman M., Kwon S., and Wiqvist N. The effect of prostaglandin E₁ on human pregnant myometrium in vivo. In: Prostaglandins, Proc. 2nd Nobel Symp., Stockholm, June 1966, ed. by S. Bergström and B. Samuelsson, pp. 93-96, Almquist and Wiksell, Stockholm; Interscience, New York, 1967.
66. Roth-Brandel U., Bygdeman M., Wiqvist N., and Bergström S. Prostaglandins for induction of therapeutic abortion. *Lancet* 1: 190-191, 1970.
67. Karim S.M.M., and Filshie G.M. Therapeutic abortion using prostaglandin F_{2α}. *Lancet* 1: 157, 1970.
68. Wiqvist N., and Bygdeman M. Therapeutic abortion by local administration of prostaglandins. *Lancet* 2: 716-717, 1970.
69. Bygdeman M., Beguin N., Topozada M., Wiqvist N., and Bergström S. Intra-uterine administration of 15(S)-15 Methyl-PGF_{2α} for induction of abortion. *Lancet* I: 13-36, 1972.
70. Bygdeman M., Green K., Topozada M., Wiqvist N., and Bergström S. The influence of prostaglandin metabolites on the uterine response to PGF_{2α}. A clinical and pharmacokinetic study. *Life Sci.* 14: 521-531, 1974.
71. Bygdeman M., Martin J.N., Wiqvist N., Gréen K., and Bergström S. Reassessment of systematic administration of prostaglandins for induction of midtrimester abortion. *Prostaglandins* 8: 157-169, 1974.
72. Bygdeman M., Gréen K., Lundström V., Ramadan M., Fotiou S., and Bergström S. Induction of abortion by vaginal administration of 15(S)15-methyl prostaglandin F_{2α} methyl ester. A comparison of two delivery systems. *Prostaglandins* 12: 27-51, 1976

73. Bygdeman M., Ganguli A., Kinoshita K., and Lundström V. Development of a vaginal suppository suitable for single administration of interruption of second trimester pregnancy. *Contraception* 15: 129-141, 1977.
74. Gréen K., Vesterqvist O., Bygdeman M., Christensen N.J., and Bergström S. Plasma levels of 9-deoxy-16,16-dimethyl-9-methylene-PGE₂ in connection with its development as an abortifacient. *Prostaglandins* 24: 451-466, 1982.
75. Nugteren D.H., Vonkeman H., and van Dorp D.A. Non-enzymatic conversion of all-cis 8,11,14-eicosatrienoic acid into prostaglandin E₂. *Receil Travaux Chim. Pays-Bas* 86: 1237-1245. 1967.