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The 1982 Nobel Prize in Medicine Recognizes the Impact of Prostaglandin Research by S. K. Bergström, B. I. Samuelsson, and J. R. Vane

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The 1982 Nobel prize in physiology or medicine was shared by Sune K. Bergström, age 66, and Bengt I. Samuelsson, age 48, both of the Karolinska Institutet, Stockholm, Sweden, and by John R. Vane, age 55, Wellcome Research Foundation, Beckenham, England.

Previous reports on Nobel prizes[1-3] used citation analysis to provide a documentary account of the field represented. Recently, we amplified these discussions by using research front data to determine the place the award-winning work occupies on the worldwide map of science. Briefly, research fronts are identified by groups of current papers that cite clusters of earlier, "core" papers.[4]

We are covering the 1982 awards in five separate essays. The first dealt with the work of physics laureate Kenneth G. Wilson.[5] The second focused on the work of chemistry prizewinner Aaron Klug.[6] Future essays will cover the prizes in economics and in literature.

Before discussing the 1982 prize in medicine, let me reiterate that citation analysis cannot *predict* Nobel laureates. It is true that citation analysis can help identify those individuals *of Nobel class*. And co-citation analysis does provide a modeling technique for forecasting the growth and development of specialties or disciplines. Indeed, we have seen that research front analysis helps identify the fields that are *eventually* acknowledged with a Nobel prize. But without confidential information it would be difficult to predict which field or individual will be recognized in a particular year.

Bergström, Samuelsson, and Vane were awarded the 1982 prize for their discoveries involving prostaglandins (PGs) and related substances.[7] As is often the case, they previously shared (in 1977) the Albert Lasker Basic Medical Research Award.[8]

PGs, of which there are many types, are hormone-like fatty acids. They are formed in the membranes of cells throughout the body—especially during times of illness, stress, or injury.[9] PGs affect the nervous, reproductive, gastrointestinal, and renal systems, as well as the regulation of body fluids and temperature and the body's defense mechanisms, such as inflammation.

PGs were first discovered in 1930 by two gynecologists, Raphael Kurzrok and Charles C. Lieb, both of Columbia University.[10] They observed a marked responsiveness of uterine smooth muscle to an as yet unidentified substance in semen.[11] However, they believed that the activity they were measuring was due to acetylcholine. It was Ulf S. von Euler, Karolinska Institutet, who first realized that this bioactivity was not due to any known mediator or catalyst.[12] By 1935, von Euler showed that the mysterious substance in semen affected numerous types of smooth muscles, and could lower the blood pressure of laboratory animals.[13,14] At that time, von Euler thought its presence in semen resulted from its production in the prostate. Thus, he named the compound "prostaglandin."[15] It was von Euler who, in 1947, urged Bergström to take up the formidable task of characterizing prosta-

glandin's chemical structure.[16] Significantly, von Euler shared a 1970 Nobel prize with Julius Axelrod, National Institutes of Health, Bethesda, Maryland, and Bernard Katz, University College, London, for work on neurotransmitters.

Bergström quickly demonstrated that the active principle in PGs was a new type of highly active, lipid-soluble, unsaturated fatty acid.[17] Later known as arachidonic acid, this chain of hydrocarbon molecules forms part of the structure of cellular membranes. It took Bergström and his colleagues about ten years to isolate pure crystals of two types of PG.[18-21] In 1962, he and his colleagues at Karolinska reported the chemical structure of three PGs.[22] It was this crucial breakthrough for which Bergström was recognized by the Nobel committee.[7]

One of the coauthors of the landmark 1962 paper was Bergström's student, Bengt Samuelsson, who subsequently participated in the structural elucidation of other types of PGs. In 1962, Samuelsson, Bergström, and others also collaborated on procedures by which all known prostaglandins can be isolated and identified.[23] A year later, Samuelsson reported improvements in these procedures,[24] and in 1964 he and Krister Grēen, Karolinska, succeeded in developing a method of quantifying the production of PGs in the body by measuring their metabolites—the products of their breakdown—in blood or urine.[25] That same year, Samuelsson again collaborated with Bergström, as well as with Henry Danielsson, Karolinska, on a detailed elucidation of the oxygenation of arachidonic acid.[26]

After setting up his own laboratory, Samuelsson began a series of investigations into the formation of PGs, and their consumption by enzymes after only a few minutes of existence.[27] This direction was suggested in part by a 1967 paper[28] coauthored by John R. Vane and Sergio H. Ferreira, University of São Paulo, Brazil, and a 1969 paper[29] by Vane and Priscilla J. Piper, then of Royal College of Surgeons, London. The former paper showed that PGs were inactivated in a few seconds upon passage through the pulmonary circulation. The latter paper reported the discovery of an unidentified substance that caused contractions in strips of aorta material from laboratory rabbits. Vane and Piper also found that anti-inflammatory agents, such as aspirin, inhibited the release of PGs.[29]

Acting on these and other results, in 1973 Samuelsson coauthored a paper with Mats Hamberg, Karolinska, showing that an endoperoxide compound is formed as an intermediate step in the process of prostaglandin synthesis.[30] Another paper by Samuelsson and several Karolinska colleagues, published in 1974, reported the isolation of two endoperoxides, and elucidated their structure.[31] These endoperoxides caused blood platelets to clump together, or aggregate. They also caused a strip of rabbit aorta to contract—although hundreds of times less strongly than the "rabbit-aorta contracting substance" found by Vane and Piper.[29,31] Later that same year, the results of an investigation by Samuelsson and Hamberg on the oxygenation of arachidonic acid in human platelets provided evidence that endoperoxides play a direct role in the regulation of cellular functions.[32] We reported this paper as one of the 1974 articles most cited during 1974.[33] This type of study, incidentally, has proved to be one of the strongest predictive indicators derived from chronological citation studies.

Hamberg, Samuelsson, and Jan Svensson, also of Karolinska, next went on to show that PG synthesis stops almost completely at the endoperoxide stage when aspirin or indomethacin, an aspirin-like drug, is taken.[34] In early 1975, Samuelsson and colleagues reported the results of a further study into the mechanism of action of endoperoxides in platelet aggregation.[35] By mid-1975, Samuelsson's years of research on PG intermediates bore fruit in a breakthrough paper entitled "Thromboxanes: a new group of biologically active compounds

derived from prostaglandin endoperoxides."[36] Coauthored with Hamberg and Svensson, the paper reported the discovery of thromboxane A_2, the unstable intermediate formed during the conversion of prostaglandin G_2 into thromboxane B_2. From the time of its publication through 1983, it has received 1,330 citations, according to *Science Citation Index®* (*SCI®*). This paper was featured as a *Citation Classic™* last year in *Current Contents®/Life Sciences*.[37] Thromboxane A_2 proved to be the mysterious substance that so powerfully contracted rabbit aorta tissue and caused blood platelets to clump together, as reported in the 1974 paper on the isolation and structure of two new endoperoxides.[31]

While Samuelsson studied and clarified the biological processes of PG formation, Vane was investigating the role PGs play in the body. The 1967 paper on the disappearance of PGs in the pulmonary circulation,[28] a *Citation Classic*,[38] also confirmed that PGs are released into the venous bloodstream when the spleen contracts. As a direct result of his interest in the release and fate of PGs in the body, and of his discovery of the rabbit-aorta contracting substance in 1969,[29] Vane was led to the idea that aspirin might interfere with the biosynthesis of PGs.[39] In a 1971 article in *Nature New Biology*, he clearly demonstrated this inhibition in cell-free preparations, and proposed that the therapeutic effects of aspirin and aspirin-like drugs are due to their ability to inhibit the enzymes that generate PGs.[40] This *Citation Classic*[41] was cited over 2,570 times by the end of 1983. It was also among the 25 1971 articles most cited in 1971 and 1972.[42]

Another article published in the same issue of *Nature New Biology*, coauthored by Vane, Ferreira, and Salvadore Moncada while they were at the Royal College of Surgeons, London, showed that aspirin and indomethacin prevent the release of PGs from the spleen, providing further support, *in vivo*, for the finding in isolated enzyme preparations.[43] This paper was also among the 25 most-cited papers of 1971.[42] The discovery of the basis of aspirin's therapeutic activity is one of the major accomplishments for which Vane was cited by the Nobel committee, which credited him with providing a powerful approach to understanding the possible role PGs play in a variety of biological events, including, for example, rheumatoid arthritis.[44]

Vane's other major accomplishment cited by the Nobel committee was his discovery of prostacyclin and its properties. Prostacyclin is also a PG derived from arachidonic acid, but has the opposite effect of thromboxane—rather than promoting the aggregation of platelets, it inhibits their clumping together.[44] Thromboxane and prostacyclin carry on a delicate balancing act to regulate clot formation. They are under study for possible use in the prevention of heart disease and stroke.

As already indicated by data for specific papers, it is somewhat redundant to say that these scientists are highly cited. Bergström's work, collectively, has been cited at least 3,600 times since 1955. He was among the 250 most-cited primary authors for the period from 1961 through 1975.[45] Among his most-cited works, Bergström's earliest papers deal with rat liver bile acids[46] and steroids.[47] By 1959, however, he had published a paper on the effects of an infusion of prostaglandin E in volunteer subjects,[48] coauthored with von Euler and several other Karolinska colleagues. In 1963, Bergström collaborated with Samuelsson, J. Sjövall, and R. Ryhage on a paper elucidating the structures of three types of prostaglandin.[49] Bergström's most-cited paper is a major review of the PG literature[50] that has received 660 citations since its publication in 1968. The paper was also among the most-cited articles of the 1960s.[51] A year earlier, Bergström wrote a comprehensive review for *Science*.[52]

Samuelsson's work has been cited explicitly over 17,000 times since 1955, the earliest year for which *SCI* data is available at present. He was identified as

one of the 300 most-cited authors for the period 1961 to 1976,[53] and also one of the 1,000 authors most-cited from 1965 through 1978.[54] Together with several Karolinska colleagues, he, too, has written a major review of PGs, covering their biosynthesis, how they are metabolized, general considerations concerning their quantitative analysis, and other characteristics.[55] He is also responsible for describing the most recently discovered members of the arachidonic acid family: leukotrienes, which contribute to inflammation, antibody production, and immune response. A paper he coauthored in 1979 with Robert C. Murphy, University of Colorado Medical School, Denver, and Sven Hammarström, Karolinska, identifies a chemical found in tumor cells as a leukotriene.[56] The paper is one of the most-cited 1979 life sciences articles.[57]

Vane's work has received over 15,400 citations from 1955 through 1983. Like Samuelsson, Vane was also identified in two of our earlier studies of most-cited authors.[53,54] Among the earliest of Vane's highly cited papers is a 1957 article reporting an improved method of detecting the presence of an amine compound (5-hydroxytryptamine) in solution.[58] He continued in this line of research, and in 1960 published an article on tryptamine receptors.[59] In 1969, Vane reviewed the development of his biological assay method known as the "blood-bathed organ technique."[60] In this technique, preparations of isolated organs are continuously bathed in a stream of blood from an anesthetized animal. The article discusses the application of the technique in the determination of the distribution and eventual fate of various hormones released into the bloodstream.

The paper reporting the discovery of prostacyclin, published in *Nature* in 1976, was coauthored by Vane and Wellcome Research Laboratory colleagues Moncada, R. Gryglewski, and S. Bunting.[61] It has been cited over 1,325 times. It is one of the most-cited papers published in 1976.[62] Indeed, it is already among the 20 most-cited articles *Nature* has ever published.[63] In fact, three more articles by Vane and colleagues,[64,65] including one reporting that prostacyclin protects arterial walls from the deposition of platelet thrombi,[66] were also identified in our study of the 1976 literature.[62] Another *Citation Classic*[67] is on a 1977 paper by Vane and colleagues that discussed the function of prostacyclin in the body.[68] Along with three others by his group,[69-71] it was among the most-cited 1977 articles.[72] Other papers by Vane's group[73,74] were included in our list of 1978 papers,[75] while still another paper[76] appears in the list for 1979.[57]

Figure 1 presents a flowchart, or microhistory, of the field of prostaglandins. Each box in the figure represents a research front. Both the title of the front and the number of core articles on which each front is based are indicated. The number of citing documents is also shown. Briefly, the configuration of the string is determined by the continuity of the core literature from year to year.[77] If any core document in a research front continues to achieve the required thresholds in an adjacent year, a cluster string is formed.

The paper on the enzymatic formation of prostaglandin E_2 by Bergström, Samuelsson, and Danielsson[26] is part of the core literature in the following research fronts: "Prostaglandin synthesis" (1977), "Synthesis and biological properties of prostaglandins and thromboxanes" (1978), "Pharmacology of prostaglandins" (1979), "Prostaglandin effect on inflammation" (1980), and "Factors affecting prostaglandin synthesis" (1981).

A 1965 article by Samuelsson on prostaglandin E_1[78] appears in the 1978 research front mentioned above. An article coauthored by Samuelsson[79] is part of the core literature for the research front "Prostaglandin biosynthesis" (1976). Another paper coauthored by Samuelsson[80] appears in the following research fronts: "Prostaglandin hydroperoxidase and prostaglandin endoperoxide synthetase" (1979), "Free radical

Figure 1: A microhistory of the field of prostaglandins. Numbers at the bottom of each box refer to the number of cited/citing documents for each research front. a = research fronts whose core literature includes papers by Bergström; b = those fronts whose core literature includes papers by Samuelsson; c = those fronts whose core literature includes papers by Vane.

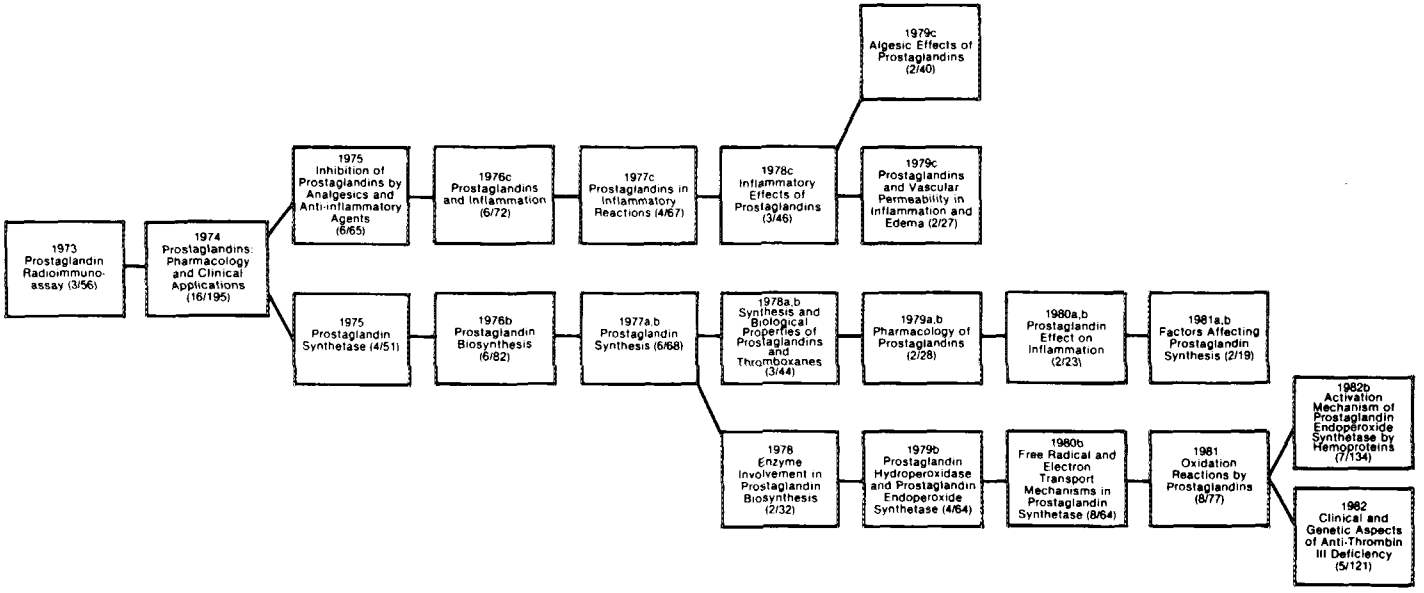
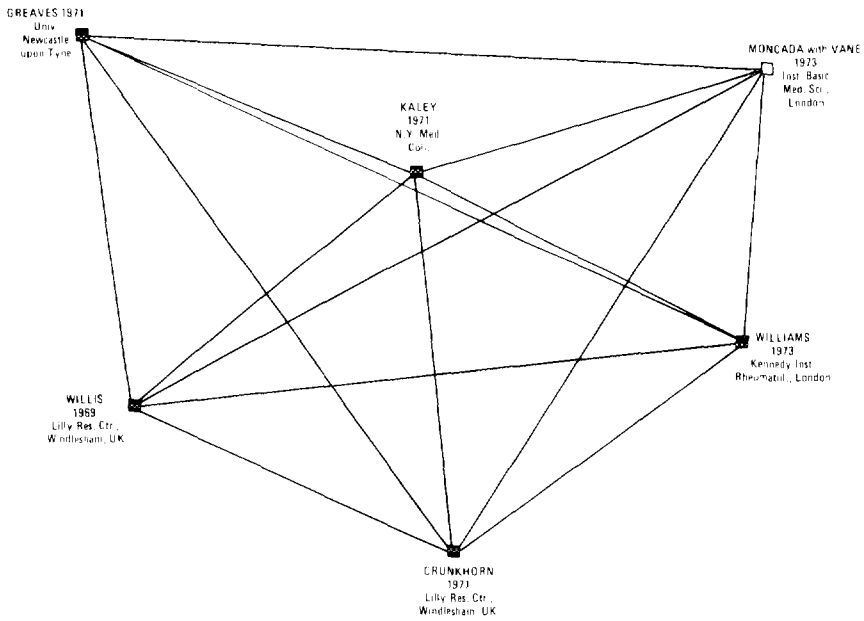


Figure 2: Multidimensional scaling map showing co-citation links between core papers of the 1976 *SCI*® research front #76-0869, "Prostaglandins and inflammation." See key for bibliographic data.



KEY

Crunkhorn P & Willis A L. Cutaneous reactions to intradermal prostaglandins. *Brit. J. Pharmacol.* 41:49-56, 1971.

Greaves M W, Sondergaard J & McDonald-Gibson W. Recovery of prostaglandins in human cutaneous inflammation. *Brit. Med. J.* 2:258-60, 1971.

Kaley G & Weiner R. Prostaglandin E_1: a potential mediator of the inflammatory response. *Ann. NY Acad. Sci.* 180:338-50, 1971.

Moncada S, Ferreira S H & Vane J R. Prostaglandins, aspirin-like drugs and the oedema of inflammation. *Nature* 246:217-9, 1973.

Williams T J & Morley J. Prostaglandins as potentiators of increased vascular permeability in inflammation. *Nature* 246:215-7, 1973.

Willis A L. Letter to editor. (Parallel assay of prostaglandin-like activity in rat inflammatory exudate by means of cascade superfusion.) *J. Pharm. Pharmacol.* 21:126-8, 1969.

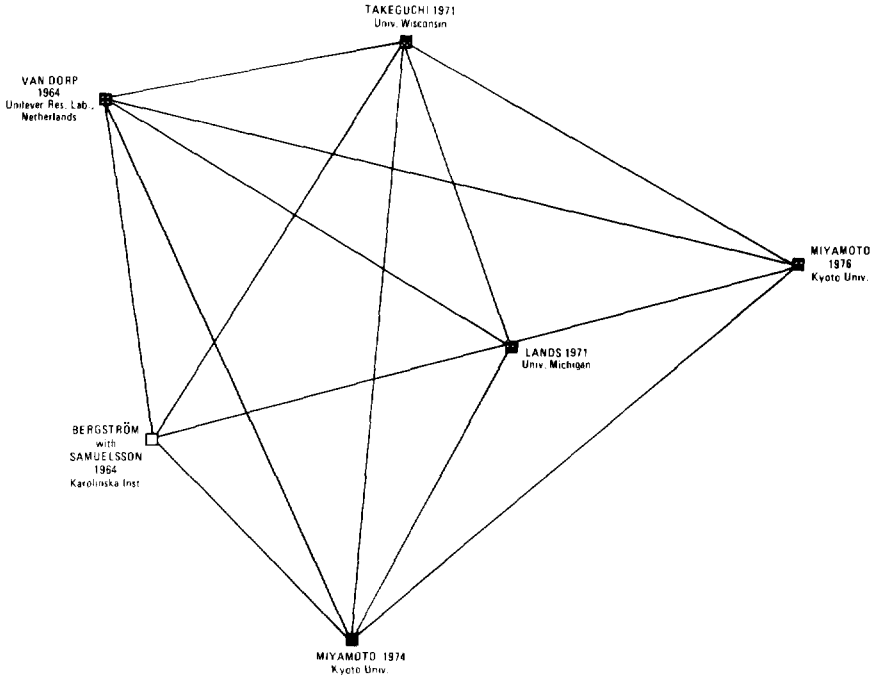
and electron transport mechanisms in prostaglandin synthetase" (1980), and "Activation mechanism of prostaglandin endoperoxide synthetase by hemoproteins" (1982). Data for 1983 research fronts were not available at the time this essay was written.

Two papers by the Vane group also occur in the core literature of research fronts in Figure 1, from 1976 through 1979. One[81] is included in the core literature of the following fronts: "Prostaglandins and inflammation" (1976), "Prostaglandins in inflammatory reactions" (1977), "Inflammatory effects of prostaglandins" (1978), and "Prostaglandins and vascular permeability in inflammation and edema" (1979). The other paper by the Vane group[82] occurs in the core literature of the 1979 front, "Algesic effects of prostaglandins."

A multidimensional scaling map of the core literature of the 1976 *SCI* front, "Prostaglandins and inflammation," is presented in Figure 2. The map includes a paper by Vane and colleagues.[81] Figure 3 presents a similar map for the 1977 *SCI* front named "Prostaglandin synthesis," which includes the enzymatic formation paper by Bergström, Samuelsson, and Danielsson.[26]

In their Nobel lectures, the 1982 laureates mention several of the workers whose papers appear in Figures 2 and 3:

Figure 3: Multidimensional scaling map of the 1977 *SCI*® research front #77-0535, "Prostaglandin synthesis," showing links between core papers. Consult key for bibliographic information.



KEY

Bergström S, Danielsson H & Samuelsson B. The enzymatic formation of prostaglandin E_2 from arachidonic acid. Prostaglandins and related factors. 32. *Biochim. Biophys. Acta* 90:207-10, 1964.

Lands W, Lee R & Smith W. Factors regulating the biosynthesis of various prostaglandins. *Ann. NY Acad. Sci.* 180:107-22, 1971.

Miyamoto T, Ogino N, Yamamoto S & Hayaishi O. Purification of prostaglandin endoperoxide synthetase from bovine vesicular gland microsomes. *J. Biol. Chem.* 251:2629-36, 1976.

Miyamoto T, Yamamoto S & Hayaishi O. Prostaglandin synthetase system—resolution into oxygenase and isomerase components. *Proc. Nat. Acad. Sci. US* 71:3645-8, 1974.

Takeguchi C, Kohno E & Sih C J. Mechanism of prostaglandin biosynthesis. I. Characterization and assay of bovine prostaglandin synthetase. *Biochemistry* 10:2372-6, 1971.

Van Dorp D A, Beerthuis R K, Nugteren D H & Vonkeman H. The biosynthesis of prostaglandins. *Biochim. Biophys. Acta* 90:204-7, 1964.

D.A. Van Dorp, R.K. Beerthuis, D.H. Nugteren, and H. Vonkeman, Unilever Research Laboratory, the Netherlands, and A.L. Willis, Syntex Research, Palo Alto, California. The core paper by the Van Dorp group,[83] listed in Figure 3, puts forward essentially the same hypothesis concerning the synthesis of prostaglandins as did Bergström, Samuelsson, and Danielsson in the enzymatic formation paper.[26] Willis has two core papers in Figure 2. One, coauthored with P. Crunkhorn when they were together at the Lilly Research Centre, Windlesham, England, concerned the effects of PGs on the blood vessels in the skin.[84] The other, authored by Willis alone, describes modifications of Vane's cascade bioassay procedure, used to detect the presence of PGs.[85]

Almost 40 years have elapsed since von Euler convinced Bergström to keep prostaglandin research alive, despite the inherent difficulties of working with

such a transient substance—and in spite of such distractions as antibiotics, steroid hormones, and World War II.[10] The perseverance of basic research pioneers such as Bergström, Samuelsson, and Vane has paid off. This is reflected in the explosive growth of the field of prostaglandins. And it is remarkable that, as more research is done, the more diverse and crucial the function of PGs seems to be. Indeed, the study of PGs has provided a basis for the development of new knowledge and therapy in many fields of medicine.

Those who select the Lasker and other awards take special pride in anticipating the Nobel prize selections. It is with some understandable pride, then, that we recall that the many citational indicators in which the work of this new crop of winners appeared long preceded their selection by the Nobel committee. Undoubtedly, there is always an element of self-consciousness in choosing candidates from one's own country or institution. But unless the number of Nobel prizes is significantly expanded, there will frequently be a considerable time gap between the award and the earliest indications that the candidates are *of Nobel class.*

This may not always be the case. Considering the widespread notion that the discoveries of the 1983 Nobel prizewinner Barbara McClintock were "premature,"[86] our analysis of her work should prove interesting. Incidentally, like Bergström, Samuelsson, and Vane, McClintock also was awarded the Albert Lasker Basic Medical Research Award (in 1981)[87] prior to receiving the Nobel prize.

* * * * *

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REFERENCES

1. **Garfield E.** Are the 1979 prizewinners *of Nobel class? Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 609-17.
2. ----------. The 1980 Nobel prizewinners. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 189-201.
3. ----------. Were the 1981 prizewinners in science, economics, and literature anticipated by citation analysis? *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 551-61.
4. ----------. ABCs of cluster mapping. Parts 1 & 2. Most active fields in the life and physical sciences in 1978. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 634-49.
5. ----------. The 1982 Nobel prize in physics. *Current Contents* (50):5-14, 12 December 1983.
6. ----------. The 1982 Nobel prize in chemistry goes to structural biologist Aaron Klug. *Current Contents* (3):3-11, 16 January 1984.
7. **Oates J A.** The 1982 Nobel Prize in Physiology or Medicine. *Science* 218:765-8, 1982.
8. **Schmeck H M.** Five pioneers in medicine get Lasker awards. *NY Times* 17 November 1977, p. 23.
9. **Altman L K.** 2 Swedes and Briton win Nobel for clues to body's chemistry. *NY Times* 12 October 1982, p. A1; C3.
10. **Shodell M.** The prostaglandin connection. *Science 83* 4(2):78-82, 1983.
11. **Kurzrok R & Lieb C C.** Biochemical studies of human semen. II. The action of semen on the human uterus. *Proc. Soc. Exp. Biol. Med.* 28:268-72, 1930.
12. **Vane J R.** Personal communication. 10 February 1984.
13. **von Euler U S.** Zur Kenntnis der pharmakologischen Wirkungen von Nativsekreten und extrakten mannlicher accessorischer Geschlechtsdrusen. (Toward an understanding of the pharmacological effects of the natural secretions and extracts of the male accessory sex glands.) *Arch. Exp. Pathol. Pharmakol.* 175:78-84, 1934.
14. ----------. A depressor substance in the vesicular gland. *J. Physiol.—London* 84:21P-2P, 1935.
15. ----------. Kurze wissenschaftliche Mitteilungen. Uber die spezifische blutdrucksenkende Substanz des menschlichen Prostata- und Samenblasensekretes. (Short scientific notes. On the specific blood pressure lowering substance in human prostate and semen vesicle secretions.) *Klin. Wochenschr.* 14:1182-3, 1935.
16. **Sattaur O.** On the trail of prostaglandins. *New Sci.* 96:82-3, 1982.
17. **Bergström S.** Prostaglandinets kemi. (Chemistry of prostaglandin.) *Nord. Med.* 42:1465-6, 1949.
18. **Bergström S & Sjövall J.** The isolation of prostaglandin. *Acta Chem. Scand.* 11:1086, 1957.
19. ----------. The isolation of prostaglandin F from sheep prostate glands. *Acta Chem. Scand.* 14:1693-700, 1960.
20. ----------. The isolation of prostaglandin E from sheep prostate glands. *Acta Chem. Scand.* 14:1701-5, 1960.

21. **Bergström S, Krabisch L & Sjövall J.** Smooth muscle stimulating factors in ram semen. *Acta Chem. Scand.* 14:1706-10, 1960.
22. **Bergström S, Ryhage R, Samuelsson B & Sjövall J.** Short communications. (The structure of prostaglandin E, F_1 and F_2.) *Acta Chem. Scand.* 16:501-2, 1962.
23. **Bergström S, Dressler F, Ryhage R, Samuelsson B & Sjövall J.** The isolation of two further prostaglandins from sheep prostate glands. Prostaglandin and related factors. 8. *Ark. Kem.* 19:563-7, 1962.
24. **Samuelsson B.** Letter to editor. (Prostaglandins and related factors. 17. The structure of prostaglandin E_3.) *J. Amer. Chem. Soc.* 85:1878-9, 1963.
25. **Gréen K & Samuelsson B.** Prostaglandins and related factors: XIX. Thin-layer chromatography of prostaglandins. *J. Lipid Res.* 5:117-20, 1964.
26. **Bergström S, Danielsson H & Samuelsson B.** The enzymatic formation of prostaglandin E_2 from arachidonic acid. Prostaglandins and related factors. 32. *Biochim. Biophys. Acta* 90:207-10, 1964.
27. **Miller J A.** Nobel prize in medicine for prostaglandin discoveries. *Sci. News* 122:245, 1982.
28. **Ferreira S H & Vane J R.** Prostaglandins: their disappearance from and release into the circulation. *Nature* 216:868-73, 1967.
29. **Piper P J & Vane J R.** Release of additional factors in anaphylaxis and its antagonism by anti-inflammatory drugs. *Nature* 223:29-35, 1969.
30. **Hamberg M & Samuelsson B.** Detection and isolation of an endoperoxide intermediate in prostaglandin biosynthesis. *Proc. Nat. Acad. Sci. US* 70:899-903, 1973.
31. **Hamberg M, Svensson J, Wakabayashi T & Samuelsson B.** Isolation and structure of two prostaglandin endoperoxides that cause platelet aggregation. *Proc. Nat. Acad. Sci. US* 71:345-9, 1974.
32. **Hamberg M & Samuelsson B.** Prostaglandin endoperoxides. Novel transformations of arachidonic acid in human platelets. *Proc. Nat. Acad. Sci. US* 71:3400-4, 1974.
33. **Garfield E.** The 1974 articles most cited in 1974. *Essays of an information scientist.* Philadelphia: ISI Press, 1977. Vol. 2. p. 426-9.
34. **Hamberg M, Svensson J & Samuelsson B.** Prostaglandin endoperoxides. A new concept concerning the mode of action and release of prostaglandins. *Proc. Nat. Acad. Sci. US* 71:3824-8, 1974.
35. **Malmsten C, Hamberg M, Svensson J & Samuelsson B.** Physiological role of an endoperoxide in human platelets: hemostatic defect due to platelet cyclo-oxygenase deficiency. *Proc. Nat. Acad. Sci. US* 72:1446-50, 1975.
36. **Hamberg M, Svensson J & Samuelsson B.** Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. *Proc. Nat. Acad. Sci. US* 72:2994-8, 1975.
37. **Hamberg M.** Citation Classic. Commentary on *Proc. Nat. Acad. Sci. US* 72:2294-8, 1975. *Current Contents/Life Sciences* 26(2):19, 10 January 1983.
38. **Ferreira S H.** Citation Classic. Commentary on *Nature* 216:868-73, 1967. *Current Contents/Life Sciences* 26(51):18, 19 December 1983.
39. **Vane J R.** Adventures and excursions in bioassay: the stepping stones to prostacyclin. (Nobel lecture.) *Brit. J. Pharmacol.* 79:821-38, 1983.
40. ----------. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.* 231:232-5, 1971.
41. ----------. Citation Classic. Commentary on *Nature New Biol.* 231:232-5, 1971. *Current Contents/Life Sciences* 23(42):12, 20 October 1980.
42. **Garfield E.** The 25 most cited 1971 papers reveal a great deal about research in 1971. *Essays of an information scientist.* Philadelphia: ISI Press, 1977. Vol. 1. p. 496-9.
43. **Ferreira S H, Moncada S & Vane J R.** Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nature New Biol.* 231:237-9, 1971.
44. **Check W A.** Prostaglandin research captures Nobel prize. *J. Amer. Med. Assn.* 248:2212-3, 1982.
45. **Garfield E.** The 250 most-cited primary authors, 1961-1975. Part I. How the names were selected. *Essays of an information scientist.* Philadelphia: ISI Press, 1980. Vol. 3. p. 326-36.
46. **Bergström S & Danielsson H.** On the regulation of bile acid formation in the rat liver. *Acta Physiol. Scand.* 43:1-7, 1958.
47. **Bergström S & Gloor U.** Studies on the 7α-hydroxylation of taurodesoxycholic acid in rat liver homogenates. Bile acids and steroids. 18. *Acta Chem. Scand.* 9:34-8, 1955.
48. **Bergström S, Duner H, von Euler U S, Pernow B & Sjövall J.** Observations on the effects of infusion of prostaglandin E in man. *Acta Physiol. Scand.* 45:145-51, 1959.
49. **Bergström S, Ryhage R, Samuelsson B & Sjövall J.** Prostaglandins and related factors. 15. The structures of prostaglandin E_1, $F_{1\alpha}$, and $F_{1\beta}$. *J. Biol. Chem.* 238:3555-64, 1963.
50. **Bergström S, Carlson L A & Weeks J R.** The prostaglandins: a family of biologically active lipids. *Pharmacol. Rev.* 20:1-48, 1968.
51. **Garfield E.** Most-cited articles of the 1960s. 3. Preclinical basic research. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 370-8.
52. **Bergström S.** Prostaglandins: members of a new hormonal system. *Science* 157:382-91, 1967.
53. **Garfield E.** The 300 most-cited authors, 1961-1976, including co-authors at last. 1. How the names were selected. *Essays of an information scientist.* Philadelphia: ISI Press, 1980. Vol. 3. p. 538-50.
54. ----------. The 1,000 contemporary scientists most-cited 1965-1978. Part I. The basic list and introduction. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 269-78.
55. **Samuelsson B, Granström E, Gréen K, Hamberg M & Hammarström S.** Prostaglandins. *Annu. Rev. Biochem.* 44:669-95, 1975.
56. **Murphy R C, Hammarström S & Samuelsson B.** Leukotriene C: a slow-reacting substance from murine mastocytoma cells. *Proc. Nat. Acad. Sci. US* 76:4275-9, 1979.
57. **Garfield E.** The 1979 articles most cited from 1979 to 1981. 1. Life sciences. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 575-90.
58. **Vane J R.** A sensitive method for the assay of 5-hydroxytryptamine. *Brit. J. Pharm. Chem.* 12:344-9, 1957.
59. ----------. The actions of sympathomimetic amines on tryptamine receptors. (Vane J R, Wolstenholme G E W & O'Connor M, eds.) *Ciba Foundation Symposium on Adrenergic Mechanisms.* Boston: Little, Brown, 1960. p. 356-72.

60. ----------. The release and fate of vaso-active hormones in the circulation. *Brit. J. Pharmacol.* 35:209-42, 1969.
61. **Moncada S, Gryglewski R, Bunting S & Vane J R.** An enzyme isolated from arteries transforms prostaglandin endoperoxides to an unstable substance that inhibits platelet aggregation. *Nature* 263:663-5, 1976.
62. **Garfield E.** The 1976 articles most cited in 1976 and 1977. Part I. Life sciences. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 81-99.
63. ----------. *Nature*: 112 years of continuous publication of high impact research and science journalism. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 261-8.
64. **Johnson R A, Morton D R, Kinner J H, Gorman R R, McGuire J C, Sun F F, Whittaker N, Bunting S, Salmon J, Moncada S & Vane J R.** The chemical structure of prostaglandin X (prostacyclin). *Prostaglandins* 12:915-28, 1976.
65. **Needleman P, Moncada S, Bunting S, Vane J R, Hamberg M & Samuelsson B.** Identification of an enzyme in platelet microsomes which generates thromboxane A_2 from prostaglandin endoperoxides. *Nature* 261:558-60, 1976.
66. **Gryglewski R J, Bunting S, Moncada S, Flower R J & Vane J R.** Arterial walls are protected against deposition of platelet thrombi by a substance (prostaglandin X) which they make from prostaglandin endoperoxides. *Prostaglandins* 12:685-713, 1976.
67. **Moncada S.** Citation Classic. Commentary on *Lancet* 1:18-21, 1977. *Current Contents/Life Sciences* 25(41):22, 11 October 1982.
68. **Moncada S, Higgs E A & Vane J R.** Human arterial and venous tissues generate prostacyclin (prostaglandin X), a potent inhibitor of platelet aggregation. *Lancet* 1:18-21, 1977.
69. **Dusting G J, Moncada S & Vane J R.** Prostacyclin (PGX) is the endogenous metabolite responsible for relaxation of coronary arteries induced by arachidonic acid. *Prostaglandins* 13:3-15, 1977.
70. **Moncada S, Bunting S, Mullane K, Thorogood P, Vane J R, Raz A & Needleman P.** Imidazole: a selective inhibitor of thromboxane synthetase. *Prostaglandins* 13:611-8, 1977.
71. **Tateson J E, Moncada S & Vane J R.** Effects of prostacyclin (PGX) on cyclic AMP concentrations in human platelets. *Prostaglandins* 13:389-97, 1977.
72. **Garfield E.** The 1977 articles most cited from 1977 to 1979. Part 1. Life sciences. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 528-41.
73. **Armstrong J M, Lattimer N, Moncada S & Vane J R.** Comparison of the vasodepressor effects of prostacyclin and 6-oxo-prostaglandin $F_{1\alpha}$ with those of prostaglandin E_2 in rats and rabbits. *Brit. J. Pharmacol.* 62:125-30, 1978.
74. **Moncada S, Korbut R, Bunting S & Vane J R.** Prostacyclin is a circulating hormone. *Nature* 273:767-8, 1978.
75. **Garfield E.** The 1978 articles most cited in 1978 and 1979. 2. Life sciences. *Essays of an information scientist.* Philadelphia: ISI Press, 1981. Vol. 4. p. 686-95.
76. **Moncada S & Vane J R.** Arachidonic acid metabolites and the interactions between platelets and blood-vessel walls. *N. Engl. J. Med.* 300:1142-7, 1979.
77. **Garfield E.** Computer-aided historiography—how ISI uses cluster-tracking to monitor the "vital signs" of science. *Essays of an information scientist.* Philadelphia: ISI Press, 1983. Vol. 5. p. 473-83.
78. **Samuelsson B.** Letter to editor. (On the incorporation of oxygen in the conversion of 8,11,14-eicosatrienoic acid to prostaglandin E_1.) *J. Amer. Chem. Soc.* 87:3011-3, 1965.
79. **Hamberg M & Samuelsson B.** On the mechanism of the biosynthesis of prostaglandins E_1 and $F_{1\alpha}$. *J. Biol. Chem.* 242:5336-43, 1967.
80. **Marnett L J, Wlodawer P & Samuelsson B.** Co-oxygenation of organic substrates by the prostaglandin synthetase of sheep vesicular gland. *J. Biol. Chem.* 250:8510-7, 1975.
81. **Moncada S, Ferreira S H & Vane J R.** Prostaglandins, aspirin-like drugs and the oedema of inflammation. *Nature* 246:217-9, 1973.
82. **Ferreira S H, Moncada S & Vane J R.** Prostaglandins and the mechanism of analgesia produced by aspirin-like drugs. *Brit. J. Pharmacol.* 49:86-97, 1973.
83. **Van Dorp D A, Beerthuis R K, Nugteren D H & Vonkeman H.** The biosynthesis of prostaglandins. *Biochim. Biophys. Acta* 90:204-7, 1964.
84. **Crunkhorn P & Willis A L.** Cutaneous reactions to intradermal prostaglandins. *Brit. J. Pharmacol.* 41:49-56, 1971.
85. **Willis A L.** Letter to editor. (Parallel assay of prostaglandin-like activity in rat inflammatory exudate by means of cascade superfusion.) *J. Pharm. Pharmacol.* 21:126-8, 1969.
86. **Cherfas J & Connor S.** How restless DNA was tamed. *New Sci.* 100:78-9, 1983.
87. **Altman L K.** Lasker awards go to geneticist and a lab head. *NY Times* 19 November 1981, p. B2.