# Current Comments

## Aspirin: Headache or Health Promoter?

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Aspirin is the most popular drug in the world. Most people probably don't realize it's a very remarkable substance. The popularity of this drug, though, is remarkable enough. In the US alone, we take 20 to 30 billion aspirin tablets a year.[1] Nobody knows exactly how many headaches that represents. The use of aspirin for disorders other than headaches is also quite substantial. It is commonly used for fever, arthritis, and other so-called "minor" discomforts, as advertisements in the English-language press keep reminding us.

Aspirin's ubiquitous quality makes it seem to be a rather innocuous drug. But it deserves a closer look. Like any drug, aspirin can be dangerous when it's misused. Even normal dosage can cause uncomfortable side effects in some people. In some circumstances, the side effects may be dangerous. On the positive side, recent studies have suggested that this medicine-chest staple might, in some cases, *save* lives if used properly.

The active ingredient in aspirin, salicylic acid, is one of the oldest medicines in the world. In "$CH_3\ CO_2\ C_6\ H_4\ CO_2H$ (Aspirin)," a 1956 *New Yorker* article recently reprinted in his book *The Medical Detectives*,[2] science writer Berton Roueché points out that Hippocrates used salicylic acid. It occurs naturally in many plants. Hippocrates, Pliny the Elder, and Galen, among others, prescribed willow leaves and bark, madder bark, and poplar gum and bark for ailments as diverse as fever, earache, corns, and bloody wounds. Such treatments went out of fashion with the rise of the Roman Empire. Roueché adds that many North American Indian tribes, and the Hottentots of South Africa, used plants containing salicylic acid for fever and rheumatism.

Salicylic acid remained popular as a folk remedy, but it wasn't reintroduced to the scientific world until 1763. It was rediscovered by Edward Stone, an English clergyman and naturalist. It was synthesized by the German chemist Hermann Kolbe in 1874.[2]

As a result, salicylic acid, alone or combined with other substances, was once again appreciated for its analgesic, antirheumatic, and antipyretic (antifever) properties. But it had its drawbacks. It tasted very bitter and irritated the stomach. Eventually, experimenters discovered that salicylic acid's effects were milder when it was acetylated; that is, combined with the radical of acetic acid. Acetylsalicylic acid (ASA), which is the scientific name for aspirin, was discovered in impure form around 1850 by an Alsatian chemist, Charles Frédéric von Gerhardt. He didn't really appreciate the meaning of his discovery.[2] In a recent review of the chemistry of aspirin, Klaus Florey,[3] Squibb Institute for Medical Research, New Brunswick, New Jersey, notes that

ASA was rediscovered in 1859 and again in 1869 before it was discovered for the last time.

As Florey explains, Felix Hoffmann, a chemist working for Farbenfabriken Bayer, Elberfeld, Germany, synthesized ASA in the company's labs in 1897. Apparently Hoffmann wanted to help his father, who suffered from rheumatism and could no longer tolerate the form of salicylic acid then popular for the disease. Hoffmann's rediscovery was tested by Heinrich Dreser, a pharmacologist at Bayer. According to Florey, there was some internal opposition to the marketing of ASA "since it was thought that the field was already overcrowded with new drugs." But ASA was marketed in tablet form in 1899.

Hoffmann obtained a US patent for ASA in 1900. However, a trade name had to be found since acetylsalicylic acid was too hard to say or remember. Bayer hit upon a commercial name that derives from *acetyl* and the German word for salicylic acid: *spirsäure*. The new drug was known from then on as aspirin.

It's difficult to say whether the drug's easy-to-remember name contributed to its success. In any case, it became very popular. Rouechê writes that by 1935, US consumption of aspirin was four million pounds; by 1944, it was nearly double that. By mid-century, aspirin was the world's cheapest, most common drug, known in almost every country.[2]

Although aspirin has been popular worldwide for decades, it has taken researchers some time to explain how it works. Aspirin's biochemical actions aren't yet fully understood. It has been known for decades that aspirin acts directly at the site of pain or inflammation rather than on the brain. Now we know that aspirin works because it affects substances called prostaglandins (PGs). PGs are hormonelike substances that are believed to be vital in regulating the function and metabolism of cells.

PGs were discovered in human semen in 1930 by gynecologist Ralph Kurzrok and pharmacologist Charles C. Lieb, City University of New York.[4] (p. 1) The Swedish scientist Ulf S. von Euler, who, like Maurice W. Goldblatt of Britain, observed PGs independently of Kurzrok and Lieb, coined the word "prostaglandin." He called it that because he thought it came from the prostate gland.[5]

PG research was difficult to conduct in early days because the substances had to be extracted from natural sources. Despite that problem, in the late 1950s, Sune Bergström, Karolinska Institutet, Stockholm, began to report on some of PG's wide-ranging effects.[6,7] In 1966, Elias J. Corey, Harvard University, and colleagues reported the synthesis of PGs. Since then it has been relatively easy to make PGs, and research has been booming.[5] ISI/BIOMED™, our new online data base, bears this out. It lists over 40 research fronts on PGs. To give an idea of the scope of PG research, we've listed ten representative research front titles in Table 1.

**Table 1:** Selected titles of prostaglandin-related research fronts from 1980 ISI/BIOMED™.

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| Anti-inflammatory drug inhibition of prostaglandin synthesis |
| Prostaglandin control of sodium excretion |
| Prostaglandin effects on gonadotropins and ovulation |
| Analgesic activity of prostaglandins in bradykinin-induced pain |
| Prostaglandins and cancer |
| Prostaglandins and dysmenorrhea |
| Prostaglandins and labor induction |
| Prostaglandins and parturition |
| Prostaglandins and renal function |
| Prostaglandins in the circulatory system |

Among their many effects, PGs can cause pain and inflammation.[5] Aspirin reduces pain and inflammation by blocking a key enzyme which produces PGs. This discovery was reported by

J.R. Vane, Royal College of Surgeons of England, London, in 1971.[8] Vane is now with Wellcome Research Laboratories, Beckenham, Kent. By 1971, a good deal of PG research was being done. Our 1971 cluster data show two PG-related clusters, on platelet aggregation and on platelet diseases. Vane's paper helped form a third on PGs and aspirin.

Vane's paper was co-cited from 1971 through 1975, together with one key aspirin-PG paper by J.B. Smith and A.L. Willis,[9] and another by S.H. Ferreira, S. Moncada, and Vane himself.[10] Interestingly, all of these authors were with the department of pharmacology of the Royal College of Surgeons, and all three papers appeared in the same issue of *Nature*. In 1973, this co-citation triad was joined by a short review on aspirin and PGs, authored by H.O.J. Collier, Miles Laboratories Limited, Stoke Poges, Buckinghamshire.[11] Since 1975, the original Vane paper has dropped out of the co-citation cluster, leaving only the papers by Smith and Willis and by Ferreira *et al.* But Vane's paper has been cited over 1,900 times. He recently published a *Citation Classic* in *Current Contents®/Life Sciences*.[12]

The work of Vane and colleagues helped us understand how aspirin exerts its benevolent effects. But a lot of work has been done on aspirin's side effects. For example, it is well known that aspirin can upset the stomach. The manner in which aspirin breaks the gastric mucosal barrier was first outlined in 1964 by physiologist Horace W. Davenport, University of Michigan.[13] Davenport published a *Citation Classic* recently in *Current Contents/Clinical Practice*.[14]

Most people can tolerate aspirin if they don't take it on an empty stomach. For people with more sensitive stomachs, the pharmaceutical companies offer a number of alternatives. Buffered aspirin is simply aspirin mixed with antacids. This combination is supposed to reduce stomach irritation. However, there is evidence that these products don't work well. A 1980 study of plain aspirin and Bufferin, by J.W. Hoftiezer and colleagues, Veterans Administration Hospital, Columbia, Missouri, concludes that the use of these drugs at the recommended dosages for a day can significantly damage the mucosa that lines the stomach.[15] Another study, by Frank L. Lanza and co-workers, concluded that buffered aspirin offers "little or no" protection to the stomach or duodenum.[16]

But another type of aspirin-antacid combination tablet may reduce stomach damage. Some aspirin products are enteric-coated. This prevents the aspirin tablet from dissolving until it reaches the intestines. The intestinal walls are less likely to be harmed by aspirin, presumably because they are more alkaline than the stomach. Lanza's team stated that enteric-coated products may offer some protection.[16]

Acetaminophen, a drug sometimes used as an aspirin substitute, has been shown to have no ill effects on the gastrointestinal system. It relieves pain and fever, so it can be taken for a headache by people who can't tolerate aspirin. Three hundred milligrams of acetaminophen relieves pain as well as the same amount of aspirin. But acetaminophen has no definite anti-inflammatory effect. It's useless for arthritis, though it may be useful for other inflammatory conditions.[17]

Some of the over-the-counter products popularly called "aspirin" are really aspirin-acetaminophen combinations. A Consumers Union study found that they are usually more expensive than plain aspirin. But the *Consumer Reports* article also stated that these combinations relieve pain no better than plain aspirin.

For that matter, generic plain aspirin is usually less expensive than brand-name plain aspirin.[18]

More serious than upset stomach or cost is the question of whether aspirin causes major gastrointestinal damage. Scientists have suspected such an association for years, but there's still no definite answer. A review in last year's *Lancet*[19] says the evidence suggests that *heavy* aspirin use is associated with major gastrointestinal hemorrhage. This occurs in about 15 aspirin users out of every 100,000. And though the association exists, no cause-and-effect relationship has been proven.

The *Lancet* review authors, Wynne D.W. Rees and Leslie A. Turnberg, University of Manchester, also note some uncertainty about the relationship between aspirin and ulcers. Aspirin may aggravate both gastric and duodenal ulcers. And though it may *cause* gastric ulcers, there's no evidence that it causes duodenal ones.[19] The aspirin-ulcer link is strong enough for at least one doctor to have written that people with peptic ulcers should avoid aspirin.[20] And as I noted in a recent essay,[21] aspirin taken with alcohol may cause ulcers.[22,23]

As with every other drug, it is questionable whether aspirin should be taken by pregnant women. High doses of aspirin have been reported to cause birth defects, but the drug is probably not an important teratogen. Aspirin and other PG synthesis inhibitors can delay delivery. They may also affect the cardiovascular system of the fetus. The drug should probably not be used to delay delivery, at least until more studies have been done.[24]

Another controversy about aspirin concerns whether it is being overused to treat fever. Nobody questions that aspirin or other antipyretic drugs should be used to treat highly elevated body temperatures. However, some animal studies show that some microorganisms grow poorly when the body temperature is mildly elevated. Recently, Matthew Kluger and Barbara Rothenburg, University of Michigan Medical School, showed that a bacterium that causes disease in rabbits doesn't grow well at rabbit fever temperature.[25] Thus, common fever may be one of nature's defenses against infection. The suggestion is bolstered by the discovery that aspirin and similar substances affect, in culture, the antiviral substance interferon.[26]

Another fever-related controversy over aspirin concerns its link with a rare but sometimes fatal disease. Reye's syndrome strikes only one or two persons under 18 per 100,000 after their recovery from influenza or chicken pox. The disease is characterized by vomiting, changes in brain structure, and fatty degeneration of the liver. The concern over Reye's syndrome and aspirin arose when T.J. Halpin, Ohio State Department of Health, and colleagues reported a 1978-1980 study of 98 Reye's cases. Ninety-five of the cases in Ohio were associated with aspirin use. A smaller study from Michigan also pointed toward the same conclusion.[27] It's too early to say there's a definite link between aspirin and Reye's syndrome. But some pediatricians are urging caution in giving aspirin to flu and chicken pox patients.[28]

Some people are allergic to aspirin. About two to six percent of asthmatics have asthmatic reactions to aspirin ingestion. In a study of 205 aspirin-sensitive persons, Frederic Speer and coworkers, Speer Allergy Clinic, Shawnee Mission, Kansas, found that women of childbearing age are the most likely group to be aspirin-allergic. But people of either sex or any age can be aspirin-sensitive. According to Speer, the most common allergic reactions to aspirin are

skin reactions, but the literature on aspirin allergy concentrates mostly on respiratory effects.[29]

Our own data confirm this statement. Of the 3,000 research front specialties identified in ISI/BIOMED, one is concerned with "adverse pulmonary effects of aspirin and other anti-inflammatory drugs." Two co-cited papers define this research front. A 1968 paper by Samter and Beers, University of Illinois College of Medicine, reported that some other mild analgesics, though structurally unrelated to aspirin, can induce allergic symptoms comparable to aspirin's.[30] The other paper, a 1975 work by A. Szczeklik and colleagues, Copernicus Medical Academy, Krakow, Poland, suggests that aspirin and certain other drugs cause asthma by inhibiting PG synthesis.[31] The eight recent papers listed in Table 2 co-cite these two papers. Aspirin-induced asthma is the major topic of most of these.

In addition to its other pulmonary effects, aspirin may give you a runny nose. When aspirin prevents the formation of PGs, the body may produce instead a substance called HETE. Its chemical name is hydroxyeicosatetraenoic acid. According to James H. Shelhamer and co-workers, National Institute of Allergy and Infectious Diseases, HETE is a potent inducer of mucus secretion. So aspirin, though it will relieve pain and fever, may actually aggravate one cold symptom.[32]

All of these side effects may make aspirin seem like more trouble than it's worth. However, its utility for relieving headache and arthritis pain is unquestioned. And aspirin may have other as yet unproven medical benefits. For example, Edward Cotlier, Yale University, has published work which suggests that aspirin can slow or delay the formation of cataracts.[33,34]

Perhaps the most exciting use of aspirin is for cerebrovascular or cardiovascular disease. The suggestion that aspirin might prevent such disease was advanced in 1953 by Glendale, California, physician Lawrence L. Craven, writing in the *Mississippi Valley Medical Journal.*[35] He published the anecdotal observation that regular low doses of aspirin might prevent coronary thrombosis. He called for more research, but work in this field did not take off until the late 1970s.

Aspirin is known to increase bleeding time and to impair platelet aggregation. Since platelets play a role in strokes and heart attacks, it seemed possible that aspirin could help deal with these problems. Two studies strongly suggested

**Table 2:** Papers in the ISI/BIOMED ™ research front specialty on aspirin and pulmonary effects. All of these papers co-cite Samter and Beers (ref. 30) and Szczeklik *et al.* (ref. 31).


**Demeter S L, Ahmad M & Tomashefski J F.** Drug-induced pulmonary-disease. 2. Categories of drugs. *Cleveland Clin. Quart.* **46**:101-12, 1979.

**Gerber J G, Payne N A, Oelz O, Nies A S & Oates J A.** Tartrazine and the prostaglandin system. *J. Allerg. Clin. Immunol.* **63**:289-94, 1979.

**Hällerdal G, Marjanovic B & Aberg H.** Rheumatoid arthritis, immune complex disease, and hypereosinophilic syndrome. *Acta Med. Scand.* **206**:429-32, 1979.

**Lane D J.** Non-immunological mechanisms in asthma. (Weatherall D J, ed.) *Medicine 1978.* New York: Wiley, 1978. p. 340-9.

**Mathison D A & Stevenson D D.** Hypersensitivity to nonsteroidal antiinflammatory drugs: indications and methods for oral challenges. *J. Allerg. Clin. Immunol.* **64**:669-74, 1979.

**Schuhl J F & Pereyra J G.** Oral acetylsalicylic acid (aspirin) challenge in asthmatic children. *Clin. Allergy* **9**:83-8, 1979.

**Spector S L, Wangaard C H & Farr R S.** Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J. Allerg. Clin. Immunol.* **64**:500-6, 1979.

**Szczeklik A & Serwonska M.** Inhibition of idiosyncratic reactions to aspirin in asthmatic patients by clemastine. *Thorax* **34**:654-7, 1979.

that aspirin helps reduce the likelihood of stroke in patients who have had transient ischemic attacks (TIAs), which often presage stroke. In May 1977, William S. Fields and colleagues, University of Texas, reported that TIA patients given aspirin had fewer strokes, deaths, and further TIAs than patients given a placebo.[36]

Another aspirin trial, the 1978 Canadian Cooperative Study Group on stroke, examined the effects of aspirin and a drug called sulfinpyrazone, which may also help in vascular diseases. The group of men at risk for stroke, when given aspirin, had fewer strokes, TIAs, or deaths. But aspirin didn't help the women studied.[37]

Though the utility of aspirin for reducing strokes in male TIA victims is well established, its utility for heart attack patients remains unproved. Some studies of patients who had heart attacks indicate that aspirin may help prevent further cardiovascular problems. But this trend was not statistically significant. The $17 million Aspirin Myocardial Infarction Study (AMIS), begun in 1975 by the National Heart, Lung, and Blood Institute, was designed to find out once and for all. AMIS followed 4,524 heart attack patients for three years. Half the patients were given one gram of aspirin, or about three tablets per day. The rest got placebos.[38]

The AMIS results were very disappointing. The aspirin group actually had a slightly higher rate of fatal heart attacks, and a slightly higher death rate, than the placebo group. The aspirin group had a much higher incidence of gastrointestinal disorders. It had a lower rate of strokes and TIAs, but not significantly lower.[38]

AMIS didn't altogether destroy hopes that aspirin can prevent heart attacks. While AMIS was under way, it was discovered that two different prostaglandins are involved in the way aspirin affects blood clotting. Aspirin prevents platelets' formation of a clotting promoter, thromboxane $A_2$. But high doses of aspirin also block blood vessel walls' manufacture of a clotting inhibitor, prostacyclin. Critics of AMIS theorized that the subjects were getting enough aspirin to inhibit *both* substances. Perhaps if they had been given a lower dose of aspirin, it would have blocked the clotting promoter but let the clotting inhibitor do its job.[39]

A study published around the time of AMIS was similarly inconclusive, and similarly tantalizing. The Persantine-Aspirin Reinfarction Study (PARIS) compared the effects of aspirin alone, and aspirin plus a platelet inhibitor called Persantine, with placebo. PARIS, which cost $8 million, was funded by Persantine's manufacturer, Boehringer-Ingelheim Corporation.[39] Persantine is a trade name for dipyridamole. The three-year study of 2,026 patients showed that aspirin with or without Persantine seemed to prevent heart attack only slightly better than Persantine alone or placebo. However, aspirin with or without Persantine showed a significant benefit for patients who had had their heart attacks within six months of entry into the trial. The aspirin dosage was the same as that in AMIS.[40]

AMIS and PARIS left room for hope that low doses of aspirin would be helpful. Unfortunately, a British study recently reported in the *New England Journal of Medicine* states that even relatively low doses of aspirin may inhibit both the clotting inhibitor and clotting promoter.[41] A recent study by Jos Vermylen and colleagues, University of Leuven, Belgium, suggests that aspirin's effects may be too broad to be helpful. The researchers write in *Lancet* that human and *in vitro* studies hint that

a drug called UK-37 248, specifically designed to inhibit thromboxane $A_2$, may work better than aspirin for cardiovascular patients.[42]

PGs are clearly where the action is in aspirin research. They figure heavily in our ISI/BIOMED research front specialty on aspirin and pulmonary disease. They are also the subject of the second aspirin-related research front, which is entitled "Interaction of aspirin with platelets and prostaglandins." A cluster of nine highly co-cited papers defines this research front. These papers are listed in Table 3. The list explains itself. The appearance of these papers in the cluster means at least two of them were cited by the over 50 current papers on this topic. For lack of space, we're listing only ten of them in Table 4.

**Table 3:** The profile of core papers, from the ISI/BIOMED ™ cluster on aspirin, platelets, and prostaglandins.

**Baenziger N L, Dillender M J & Majerus P W.** Cultured human skin fibroblasts and arterial cells produce a labile platelet-inhibitory prostaglandin. *Biochem. Biophys. Res. Commun.* **78**:294-301, 1977.

**Burch J W, Stanford N & Majerus P W.** Inhibition of platelet prostaglandin synthetase by oral aspirin. *J. Clin. Invest.* **61**:314-9, 1978.

**Czervionke R L, Hoak J C & Fry G L.** Effect of aspirin on thrombin-induced adherence of platelets to cultured cells from the blood vessel wall. *J. Clin. Invest.* **62**:847-56, 1978.

**Kelton J G, Hirsh J, Carter C J & Buchanan M R.** Thrombogenic effect of high-dose aspirin in rabbits. *J. Clin. Invest.* **62**:892-5, 1978.

**Moncada S & Korbut R.** Dipyridamole and other phosphodiesterase inhibitors act as antithrombotic agents by potentiating endogenous prostacyclin. *Lancet* **1**:1286-9, 1978.

**Moncada S, Herman A G, Higgs E A & Vane J R.** Differential formation of prostacyclin (PGX or $PGI_2$) by layers of the arterial wall. An explanation for the anti-thrombotic properties of vascular endothelium. *Thromb. Res.* **11**:323-44, 1977.

**O'Grady J & Moncada S.** Aspirin: a paradoxical effect on bleeding time. *Lancet* **2**:780, 1978.

**Tanaka R L, Nanna D H & White H L.** Synthesis of prostaglandin 6-keto $F_{1\alpha}$ by cultured aortic smooth muscle cells and stimulation of its formation in a coupled system with platelet lysates. *Prostaglandins* **15**:399-408, 1978.

**Weksler B B, Ley C W & Jaffe E A.** Stimulation of endothelial cell prostacyclin production by thrombin, trypsin, and the ionophore A 23187. *J. Clin Invest.* **62**:923-30, 1978.

**Table 4:** Papers co-citing the papers in Table 3. This research front consists of a total of 52 papers, so for reasons of space we are displaying ten papers which mention aspirin in their titles.

**Amezcua J L, O'Grady J, Salmon A J & Moncada S.** Prolonged paradoxical effect of aspirin on platelet behaviour and bleeding-time in man. *Thromb. Res.* **16**:69-79, 1979.

**Czervionke R L, Smith J B, Fry G L, Hoak J C & Haycraft D L.** Inhibition of prostacyclin by treatment of endothelium with aspirin. *J. Clin. Invest.* **63**:1089-92, 1979.

**Harter H R, Burch J W, Majerus P W, Stanford N, Delmez J A, Anderson C B & Weerts C A.** Prevention of thrombosis in patients on hemodialysis by low-dose aspirin. *N. Engl. J. Med.* **301**:577-9, 1979.

**Jaffe E A & Weksler B B.** Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin. *J. Clin. Invest.* **63**:532-5, 1979.

**Masotti G, Poggesi L, Galanti G, Abbate R & Serneri G G N.** Differential inhibition of prostacyclin production and platelet-aggregation by aspirin. *Lancet* **2**:1213-6, 1979.

**Miwa K, Kambara H & Kawai C.** Variant angina aggravated by aspirin. *Lancet* **2**:1382, 1979.

**Rajah S M, Penny A F, Crow M J, Pepper M D & Watson D A.** The interaction of varying doses of dipyridamole and acetyl salicylic acid on the inhibition of platelet functions and their effect on bleeding time. *Brit. J. Clin. Pharmacol.* **8**:483-9, 1979.

**Siegel M I, McConnell R T & Cuatrecasas P.** Aspirin-like drugs interfere with arachidonate metabolism by inhibition of the 12-hydroperoxy-5,8,10,14-eicosatetraenoic acid peroxidase activity of the lipoxygenase pathway. *Proc. Nat. Acad. Sci. US* **76**:3774-8, 1979.

**Vilia S & Gaetano G D.** Bleeding time in laboratory animals. IV. Effects of prostacyclin, pyrimido-pyrimidine compounds and aspirin in rats. *Thromb. Res.* **15**:727-32, 1979.

**Vilia S, Livio M & Gaetano G D.** The inhibitory effect of aspirin on platelet and vascular prostaglandins in rats cannot be completely dissociated. *Brit. J. Haematol.* **42**:425-31, 1979.

Since heart attacks are the nation's number one killer, it would be quite a discovery if a substance as simple and cheap as aspirin were effective in cutting the death toll. If other solutions are found, the aspirin-PG link will have provided essential clues. Of course, we don't know enough about aspirin to say that it will ward off cerebrovascular or cardiovascular problems for people who haven't had TIAs or heart attacks in the first place. It's important to make this point because some doctors fear that lay persons may begin treating themselves with aspirin. This view may derive from the widespread notion that aspirin is an innocuous drug. But as we have seen, its widespread popularity, its effects, and its side effects make it formidable indeed.

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**REFERENCES**


1. **Ingelfinger F J.** The side effects of aspirin. *New Engl. J. Med.* 290:1196-7, 1974.
2. **Roueché B.** *The medical detectives.* New York: Times Books, 1980. 372 p.
3. **Florey K.** Aspirin. (Florey K, ed.) *Analytical profiles of drug substances.* New York: Academic Press, 1979. Vol. 8. p. 1-46.
4. **von Euler U S & Eliasson R.** *Prostaglandins.* New York: Academic Press, 1967. 164 p.
5. **Wasserman M A.** Prostaglandins. *Amer. Pharm.* NS19:15-9, 1979.
6. **Bergström S, Duner H, v. 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.
7. **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.
8. **Vane J R.** Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nature New Biol.* 231:232-5, 1971.
9. **Smith J B & Willis A L.** Aspirin selectively inhibits prostaglandin production in human platelets. *Nature New Biol.* 231:235-7, 1971.
10. **Ferreira S H, Moncada S & Vane J R.** Indomethacin and aspirin abolish prostaglandin release from the spleen. *Nature New Biol.* 231:237-9, 1971.
11. **Collier H O J.** Prostaglandins and aspirin. *Nature* 232:17-9, 1971.
12. **Vane J R.** Citation Classic. Commentary on *Nature New Biol.* 231:232-5, 1971. *Current Contents/Life Sciences* 23(42):12, 20 October 1980.
13. **Davenport H W.** Gastric mucosal injury by fatty and acetylsalicylic acids. *Gastroenterology* 46:245-53, 1964.
14. ----------. Citation Classic. Commentary on *Gastroenterology* 46:245-53, 1964. *Current Contents/Clinical Practice* 9(7):16, 16 February 1981.
15. **Hoftiezer J W, O'Laughlin J C & Ivey K J.** Comparison of the acute effects of regular aspirin, Bufferin, and acetaminophen on human gastroduodenal mucosa. *Gastroenterology* 78:1183, 1980.
16. **Lanza F L, Royer G L & Nelson R S.** Endoscopic evaluation of the effects of aspirin, buffered aspirin and enteric-coated aspirin on gastric and duodenal mucosa. *N. Engl. J. Med.* 303:136-8, 1980.
17. **Cooper S A.** Comparative analgesic efficacies of aspirin and acetaminophen. *Arch. Intern. Med.* 141(3):282-5, 23 February 1981.
18. Is Tylenol (et al) any better than aspirin? *Consumer Rep.* 41: 560-2, 1976.
19. **Rees W D W & Turnberg L A.** Reappraisal of the effects of aspirin on the stomach. *Lancet* 2:410-3, 1980.
20. **Spiro H M.** Aspirin is dangerous for the peptic ulcer patient. (Ingelfinger F J, Ebert R V, Finland M & Relman A S, eds.) *Controversy in internal medicine II.* Philadelphia, PA: Saunders, 1974. p. 500-8.
21. **Garfield E.** All about ulcers, antacids, and how little we know. *Current Contents* (45):5-12, 10 November 1980.
22. **Robert A, Nezamis J E, Hanchar A J & Lancaster C.** Aspirin combined with alcohol is ulcerogenic. *Gastroenterology* 78:1245, 1980.
23. **Davenport H W.** Gastric mucosal hemorrhage in dogs: effects of acid, aspirin, and alcohol. *Gastroenterology* 56:439-49, 1969.

24. **Rudolph A M.** Effects of aspirin and acetaminophen in pregnancy and in the newborn. *Arch. Intern. Med.* 141(3):358-63, 23 February 1981.
25. **Kluger M J & Rothenburg B A.** Fever and reduced iron: their interaction as a host defense response to bacterial infection. *Science* 203:374-6, 1979.
26. **Pottathil R, Chandrabose K A, Cuatrecasas P & Lang D J.** Establishment of the interferon-mediated antiviral state: role of fatty acid cyclooxygenase. *Proc. Nat. Acad. Sci. US* 77:5437-40, 1980.
27. **Halpin T J, Holtzhauer F & Hayner N.** Reye syndrome—Ohio, Michigan. *Morbid. Mortal. Weekly Rep.* 29:532-9, 1980.
28. Pediatricians urge caution on aspirin use. *Med. World News* 22(3):31, 2 February 1981.
29. **Speer F, Denison T R & Baptist J E.** Aspirin allergy. *Ann. Allergy* 46(3):123-6, March 1981.
30. **Samter M & Beers R F.** Intolerance to aspirin: clinical studies and consideration of its pathogenesis. *Ann. Intern. Med.* 68:975-83, 1968.
31. **Szczeklik A, Gryglewski R J & Czernlawska-Mysik G.** Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *Brit. Med. J.* 1:67-9, 1975.
32. Aspirin, other drugs linked to runny noses. *Chem. Eng. News* 59(11):8, 16 March 1981.
33. **Cotlier E.** Aspirin effect on cataract formation in patients with rheumatoid arthritis alone or combined with diabetes. *Int. Ophthalmol.* 3(3):173-7, 1981.
34. **Cotlier E & Sharma Y R.** Aspirin and senile cataracts in rheumatoid arthritis. *Lancet* 1(8215):338-9, 7 February 1981.
35. **Craven L L.** Experiences with aspirin (acetylsalicylic acid) in the nonspecific prophylaxis of coronary thrombosis. *Miss. Valley Med. J.* 75:38-44, 1953.
36. **Fields W S, Lemak N A, Frankowski R F & Hardy R J.** Controlled trial of aspirin in cerebral ischemia. *Stroke* 8:301-14, 1977.
37. **The Canadian Cooperative Study Group.** A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N. Engl. J. Med.* 299:53-9, 1978.
38. **Aspirin Myocardial Infarction Study Research Group.** A randomized, controlled trial of aspirin in persons recovered from myocardial infarction. *J. Amer. Med. Assn.* 243:661-9, 1980.
39. **Marx J L.** AMIS negative on aspirin and heart attacks. *Science* 207:859-60, 1980.
40. **Krol W F.** Persantine and aspirin in coronary heart disease. *Circulation* 62:449-61, 1980.
41. **Preston F E, Whipps S, Jackson C A, French A J, Wyld P J & Stoddard C J.** Inhibition of prostacyclin and platelet thromboxane $A_2$ after low-dose aspirin. *N. Engl. J. Med.* 304(2):76-9, 8 January 1981.
42. **Vermylen J, Carreras L O, Schaeren J V, Defreyn G, Machin S J & Verstraete M.** Thromboxane synthetase inhibition as antithrombotic strategy. *Lancet* 1(8229):1073-5, 16 May 1981.

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We regret to announce the death on August 13, 1981, of Samuel Lazerow, ISI®'s senior vice president of administration. Lazerow's contributions to the field of library and information science were considerable. His unique career included top-level administrative positions in each of the three national libraries of the United States—the National Library of Agriculture, the National Library of Medicine, and the Library of Congress. As one of my closest friends for 30 years, he played a significant role in the development of *Current Contents*® (*CC*®) and our other ISI services. Many years ago an essay in *CC* touched on his role.[1] In the future, I will be writing more about Sam's contributions to library and information science and to ISI.

**REFERENCE**

1. **Garfield E.** Introducing Samuel Lazerow, ISI®'s vice president for administration. *Current Contents* (44):5-6, 1 November 1972.*

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