

EDITORIAL

KENNETH C. CUMMINGS III, MD, MS, FASA

Medical Director, Pre-Anesthesia Consultation Clinics; Staff Anesthesiologist, Department of General Anesthesiology, Anesthesiology Institute, Cleveland Clinic; Assistant Professor of Anesthesiology, Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland, OH

Aspirin: 4,000 years and still learning

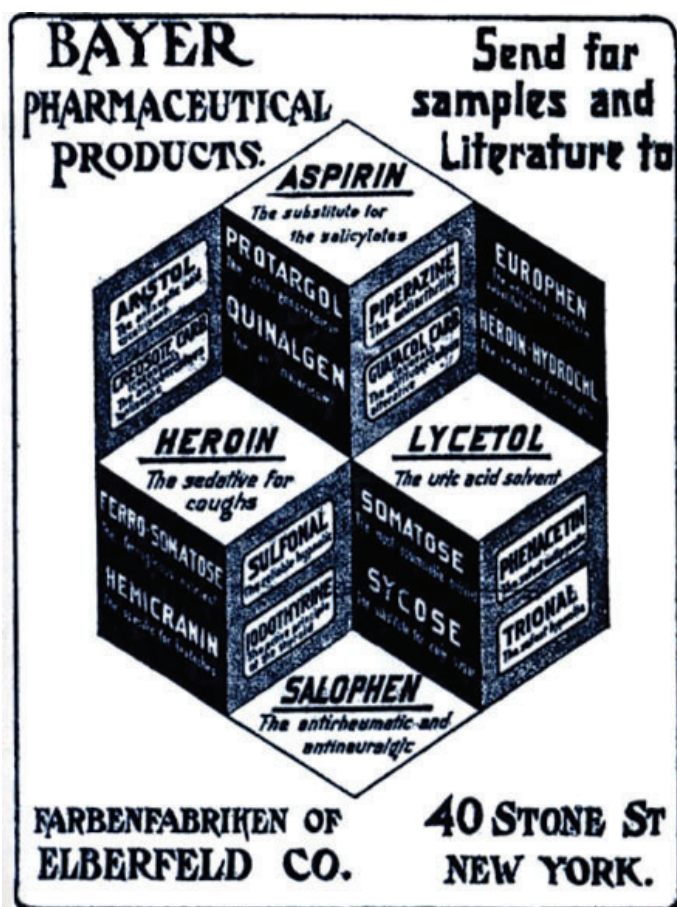


Figure 1.

ASPIRIN (ACETYLSALICYLIC ACID) and its progenitors are valuable medications with a history spanning at least 4 millennia. An enormous number of patients take aspirin for a variety of reasons, and managing their therapy around the time of surgery can be challenging, as Drs. Prabhakaran and Whinney discuss in this issue.¹ Even after 4,000

doi:10.3949/cjcm.86a.19041

years, we are still learning about these remarkable drugs.

See related article, page 518

■ LEARNING WHAT SALICYLATES ARE

Medicines made from the bark of willow trees (genus *Salix*) and other salicylate-rich plants have been used as analgesics since at least 2000 BCE. References exist on the Ebers Papyrus from Egypt (circa 1550 BCE) as well as on ancient Sumerian tablets.² It was not until the 18th century, however, that Edmund Stone identified salicin, a glycoside of salicylic acid and the active compound in willow bark extract. Searching for a way to reduce the burning throat and dyspepsia caused by salicylic acid, chemists at Friedrich Bayer & Company—the same group that popularized heroin as a “nonaddictive” form of morphine—eventually produced acetylsalicylic acid. Bayer gave the compound the brand name “Aspirin,” using “A” for acetylation, “-spir-” for *Spirea* (another common source of salicylic acid), and “-in” as a conventional drug-name ending (Figure 1).³

■ LEARNING (AND IGNORING) WHAT ASPIRIN CAN DO

In the 1940s, a general practitioner in California named Lawrence Craven recognized that many of his post-tonsillectomy patients had to be hospitalized for bleeding after he started recommending they use aspirin-containing chewing gum for pain relief.⁴ Under the then-debated hypothesis that myocardial infarction (MI) involves thrombosis, he recommended that adult men should take aspirin daily. He believed that women had lower rates of MI

because they were more likely to take aspirin, something that men did not view as a “masculine” thing to do.

In a series of letters in journals such as the *Mississippi Valley Medical Journal*,⁵ Craven reported his observations of very low rates of MI and no strokes in aspirin users. Given the nonrigorous nature of his research and the obscure journals in which he published, his findings languished for many years. Ironically, he died of an MI in 1957.

■ LEARNING HOW ASPIRIN WORKS (AND A FEW OTHER THINGS)

The history of aspirin research illustrates how the fields of hemostasis and inflammation are now linked.

In the late 1960s, Weiss et al⁶ reported that aspirin rapidly and irreversibly inhibits platelet aggregation. In parallel, using biological assays in work that eventually led to the Nobel Prize, Vane⁷ discovered that inflammation involves the de novo synthesis of prostaglandins and that aspirin directly inhibits this synthesis. Further work connecting these lines of investigation led us to understand that platelet aggregation is enhanced by the prostaglandin derivative thromboxane A₂, produced by cyclooxygenase-1, and that aspirin irreversibly inhibits this enzyme by acetylation.

■ LEARNING WHEN TO USE ASPIRIN

After decades of research ranging from the Physicians' Health Study to well-named trials such as ARRIVE, ASCEND, and ASPREE, we now know that taking daily low doses of aspirin for primary prevention can reduce the risk of cardiovascular events and may reduce the risk of colorectal cancer—but at the cost of an increased risk of bleeding.⁸

Which patients will gain the most benefit and incur the least risk is still debated. What is certain, however, is that aspirin has an important role in acute coronary syndromes, secondary prevention of MI and stroke, and prevention of thrombosis after coronary stent placement. In the perioperative setting, we are learning that aspirin may benefit patients with

myocardial injury after noncardiac surgery, a recently described clinical entity associated with surprisingly high mortality rates.^{9,10}

■ LEARNING WHEN NOT TO USE ASPIRIN

The perioperative period is a dangerous time—surgical stress, hypercoagulability, inflammation, pain, and hemodynamic changes predispose to plaque rupture and supply-demand imbalance. It is therefore logical to hope aspirin would provide protection for at-risk patients in this context.

Unfortunately, results from the second Perioperative Ischemic Evaluation trial have dampened enthusiasm.¹¹ Aspirin has now joined clonidine and beta-blockers on the list of interventions that probably do not reduce perioperative cardiovascular mortality rates. Other than protecting against stent thrombosis, aspirin's main perioperative effect is to increase bleeding. Consequently, some surgical procedures mandate withdrawal of aspirin.

■ WHAT WE STILL NEED TO LEARN

Over the years, we have learned the broad outlines of using aspirin to prevent and treat cardiovascular disease, to relieve pain and inflammation (its original purpose), and to prevent stent thrombosis.

However, many details remain to be filled in. We need to better define groups who should and should not take aspirin for primary prevention. We also need to understand aspirin's role in cancer chemoprevention, to find better ways to mitigate its undesirable effects, and to study its role in treating myocardial injury after noncardiac surgery.

Finally, we need to determine which (if any) patients without coronary stents will benefit from continuing their aspirin perioperatively or even initiating aspirin therapy preoperatively.

Will humanity still be using salicylates 4,000 years from now? Probably not. But what we have learned and will continue to learn from this remarkable group of medications will certainly inform new and better therapies in the years to come. ■

Which patients will gain the most benefit and incur the least risk is still debated

REFERENCES

1. **Prabhakaran A, Whinney C.** Should we stop aspirin before noncardiac surgery? *Cleve Clin J Med* 2019; 86(8):518–521. doi:10.3949/ccjm.86a.19036
2. **Jeffreys D.** Aspirin: The Remarkable Story of a Wonder Drug. New York: Bloomsbury; 2008.
3. **Mann CC, Plummer ML.** The Aspirin Wars: Money, Medicine, and 100 Years of Rampant Competition. New York: Alfred A. Knopf; 1991.
4. **Miner J, Hoffhines A.** The discovery of aspirin's antithrombotic effects. *Tex Heart Inst J* 2007; 34(2):179–186. PMID:17622365
5. **Craven LL.** Prevention of coronary and cerebral thrombosis. *Miss Valley Med J* 1956; 78(5):213–215. PMID:13358612
6. **Weiss HJ, Aledort LM, Kochwa S.** The effect of salicylates on the hemostatic properties of platelets in man. *J Clin Invest* 1968; 47(9):2169–2180. doi:10.1172/JCI105903
7. **Vane JR.** Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. *Nat New Biol* 1971; 231(25):232–235. PMID:5284360
8. **US Preventive Services Task Force.** Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. *Ann Intern Med* 2009; 150(6):396–404. PMID:19293072
9. **Botto F, Alonso-Coello P, Chan MT, et al.** Myocardial injury after noncardiac surgery: a large, international, prospective cohort study establishing diagnostic criteria, characteristics, predictors, and 30-day outcomes. *Anesthesiology* 2014; 120(3):564–578. doi:10.1097/ALN.000000000000113
10. **George R, Menon VP, Edathadathil F, et al.** Myocardial injury after noncardiac surgery—incidence and predictors from a prospective observational cohort study at an Indian tertiary care centre. *Medicine (Baltimore)* 2018; 97(19):e0402. doi:10.1097/MD.00000000000010402
11. **Devereaux PJ, Mrkobra M, Sessler DI, et al; POISE-2 Investigators.** Aspirin in patients undergoing noncardiac surgery. *N Engl J Med* 2014; 370(16):1494–1503. doi:10.1056/NEJMoa1401105

ADDRESS: Kenneth C. Cummings III, MD, MS, FASA, Anesthesiology Institute, E31, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; cummink2@ccf.org