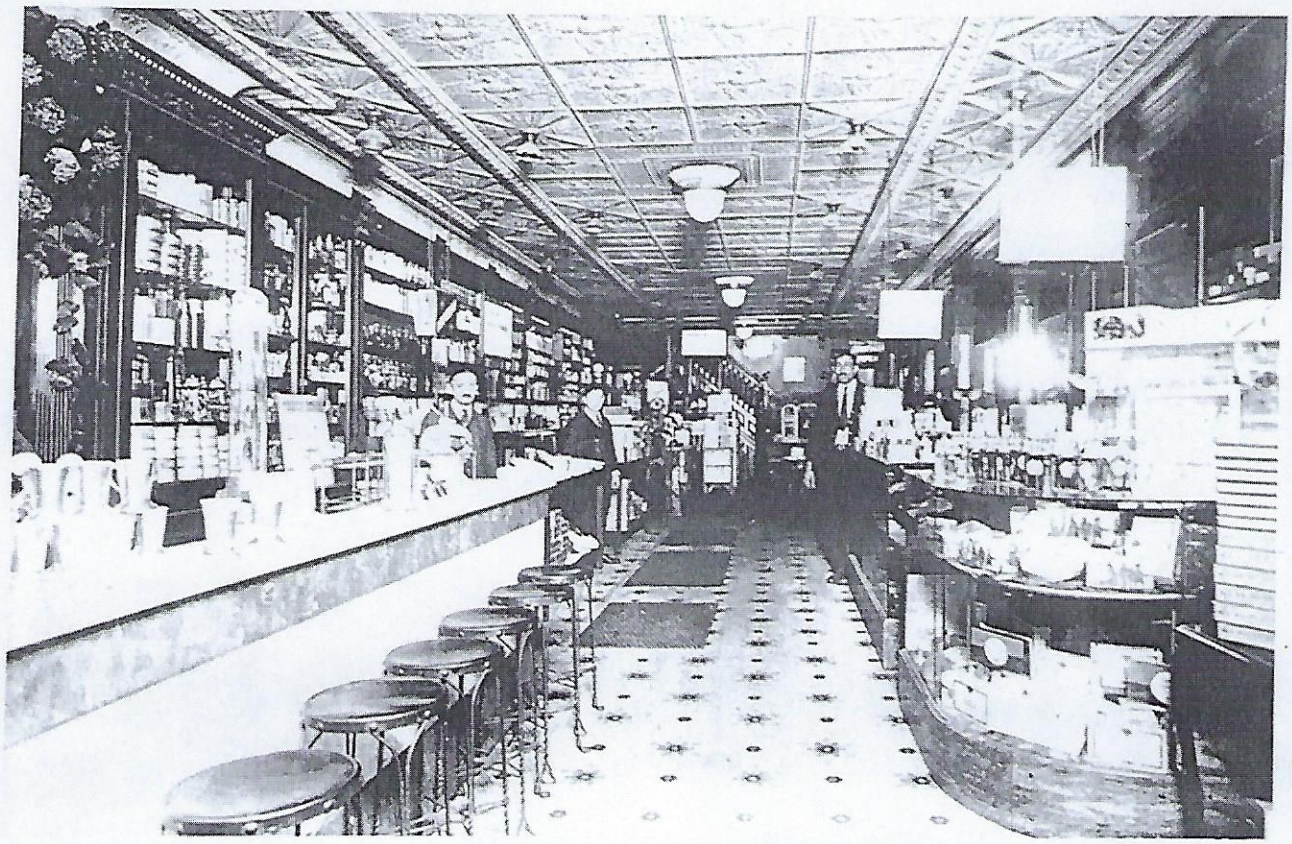
Dr. Ward

AMI Work for Advanced Biology

1. Read the following article.
2. Write a brief summary.
3. Write a 1 paragraph discussion of the importance of this scientist's work today.



■ The interior of McNeil's Drug & Prescription Store at Front and York Streets, Philadelphia, 1900. Courtesy McNeil Consumer Healthcare.

Robert L. McNeil, Jr. (1915–)

Even before aspirin was created, the active ingredient in one of today's most popular pain relievers and fever reducers, Tylenol, had been discovered. But because toxicology and pharmacology were still in their early stages in the late nineteenth century, this substance—*N*-acetyl *p*-aminophenol—was left on the shelf for over fifty years, until research in the mid-twentieth century demonstrated its efficacy and safety. In the United States its popularity can be traced to a decision made in 1954 by the New Products Committee at McNeil Laboratories to undertake the additional laboratory and clinical testing needed to gain approval for the drug from the U.S. Food and Drug Administration and then to market it.

In 1886, at the University of Strassburg, then located in Germany, two young chemists, Arnold Cahn and Paul Hepp, were asked by their professor to use the coal-tar derivative naphthalene as an "internal antiseptic" to treat a patient suffering from worms and a variety of other ailments. The patient's fever subsided—surprisingly, since naphthalene was not known to have fever-reducing, or antipyretic, properties. Cahn and Hepp suspected that the pharmacist had made an error, as indeed he had: he had sent by mistake another simple organic chemical, also derived from coal tar, acetanilide. They published a report of their finding, and a small company near Frankfurt, Kalle and Company, later taken over by Hoechst, began to manufacture a drug named Antifebrin, whose active ingredient was acetanilide.

When Antifebrin first came on the market, the Bayer Company in Elberfeld, Germany, began to look for a similar drug. Oscar Hinsberg, a chemist at Bayer, synthesized the ethyl ether of acetanilide by acetylating *p*-nitrophenol, and Bayer sold the drug, trademarked as phenacetin, from 1888 on as an antipyretic and analgesic, or pain reliever. Almost immediately physiological chemists investigating the relationships between the chemical composition and the physiological function of Antifebrin and phenacetin discovered through urinalyses that the metabolic processes of animals and humans transformed these drugs into *N*-acetyl *p*-aminophenol.

In 1893 Joseph von Mering, who was then conducting his famous research on diabetes (see Frederick Grant Banting et al., p. 52), published a clinical study of the effects of several compounds of the aminophenol structural class. Among other conclusions, he wrote (wrongly, as would later be determined) that *p*-aminophenol and *N*-acetyl *p*-aminophenol were active antipyretics but were not suitable for clinical use. One of the relatively few patients he tested with *p*-aminophenol turned blue, showing that the capacity of the patient's red blood cells to distribute oxygen to the body had been destroyed, in a condition called methemoglobinemia. In the case of *N*-acetyl *p*-aminophenol he reported no specific observations of patients, information that he had provided for the other substances he had tested.

Meanwhile acetanilide and phenacetin (which lost its status as a trade name) competed with aspirin through World War II. In 1938 the U.S. Food and Drug Administration, newly strengthened by the Food, Drug, and Cosmetic Act of that year, briefly pulled acetanilide from the market because they suspected it caused agranulocytosis, an abnormal condition of the white blood cells.

Although the law did not require companies to test products already on the market, Walter Ames Compton, director of research at Miles Laboratories in Elkhart, Indiana, recognized the critical importance of using the latest methods of pharmacology and toxicology to investigate the standard remedies like Miles's Alka-Seltzer, created before such tools were available. He also realized that in the course of time these new investigations might well lead to new or improved drugs. In 1939 he convinced Miles Laboratories and nine other companies to establish an independent institute, the Institute for the Study of Analgesic and Sedative Drugs, to conduct basic research. Although these companies had their own research laboratories, they agreed that the results generated by an outside body would be more credible to the public.

The newly founded institute hired scientists from leading medical schools to conduct investigations, among them a team investigating acetanilide and phenacetin: Leon Greenberg and David Lester of Yale University and Bernard Brodie, Julius Axelrod, and Frederick B. Flinn of New York University. (During the course of the research Brodie and Axelrod moved to the National Heart Institute at the National Institutes of Health.) Their reports showed conclusively that in humans the active metabolite of both acetanilide and phenacetin was *N*-acetyl *p*-aminophenol and that this compound accounted for the antipyretic and analgesic properties of the two drugs. Methemoglobinemia, it was found, was caused not by *N*-acetyl *p*-aminophenol but by another metabolic breakdown product of the drugs under study. The researchers also cleared all three compounds of the suspicion of causing agranulocytosis. In short, *N*-acetyl *p*-aminophenol appeared to be free from side effects that would preclude its use in normal dosage. These findings and others were presented at a one-day symposium sponsored by the Institute for the Study of Analgesic and Sedative Drugs and held in May 1951 at the Biltmore Hotel in New York City. Earlier, good reports coming out of Yale and New York Universities had led several American pharmaceutical companies to begin manufacturing products containing *N*-acetyl *p*-aminophenol, but their sales efforts were halfhearted, largely because they feared that the new products would adversely affect sales of their aspirin-based products.

The drug truly emerged from the shadows soon thereafter, when, at an American Pharmaceutical Manufacturers Association meeting, Robert L. McNeil, Jr., then vice president of McNeil Laboratories, learned more of the institute's research results in an informal discussion with Raymond L. Conklin, who was vice president of the institute as well as vice president of Ames Company, a subsidiary of Miles Laboratories, in Elkhart, Indiana. That discussion put McNeil Laboratories on a course that resulted in its all-time best-seller, Tylenol.

Robert L. McNeil, Jr., represented the third generation of his family at McNeil Laboratories. The company had evolved from a neighborhood pharmacy established in Philadelphia in 1879. Until the 1930s it had specialized in selling hundreds of drugs to physicians who dispensed them without prescription to their patients. After earning a B.S. in physiological chemistry and bacteriology at Yale University in 1936, Robert McNeil entered the business in 1937, while completing a second bachelor's degree at the Philadelphia College of Pharmacy, now University of the Sciences in Philadelphia. (He simultaneously pursued graduate studies at Temple University.) He soon was made responsible for reevaluating the company's product line, reorganizing its departments, and creating a research-and-development division to develop prescription products that would comply with the "safe for use" requirements of the federal Food, Drug and Cosmetic Act of 1938 (see Walter Campbell, p. 136).

When McNeil returned from the pharmaceutical manufacturers meeting, he had Charles F. Kade, Jr., the head of the firm's medical sciences division, and James M. Shaffer, head of its clinical investigation division, confirm the significance of Ray Conklin's verbal report on *N*-acetyl *p*-aminophenol. He then convened a meeting of the firm's New Products Committee, which included these scientists as well as his brother Henry McNeil, then vice president of marketing, and the directors of sales (David S. Lamont), advertising and promotion (John Hogan), and market planning (Douglas G. Lovell, Jr.). It was Lovell who subsequently coined the name *Tylenol* from the drug's chemical name, and Robert McNeil who suggested *acetaminophen* as the generic term.

Presented with a proposal to put *N*-acetyl *p*-aminophenol on the market, the marketing and sales executives on the New Products Committee raised the obvious question: why try to sell a drug to compete with aspirin that would cost more than aspirin? McNeil convinced the doubters by pointing out that the drug had antipyretic and analgesic properties similar to those of aspirin but did not cause the stomach irritation that aspirin often did, especially when taken too frequently—a property that had only been touched on at the symposium in New York. Furthermore, McNeil planned to aim at a different niche: developing a drug that the marketing division could promote to physicians for them to prescribe—not an over-the-counter product that would compete directly with aspirin.

Unlike many other pharmaceutical companies, McNeil Labs did not have its own aspirin product and did not have to fear such competition. For example, Sterling-Winthrop decided to rely solely on aspirin in the United States rather than adopt Panadol, an *N*-acetyl *p*-aminophenol product that its subsidiary, Bayer Ltd., had developed for the British market on the basis of the Yale and Columbia studies.

As the McNeil plan evolved, the pediatric field was targeted, with the objective of developing a liquid-dosage form for children. First McNeil's pharmacology department, headed by David Marsh, confirmed the pharmacologic and toxicologic conclusions of the Lester-Greenberg and Brodie-Axelrod-Flinn groups and others. Clinical trials of a pediatric elixir were conducted in cooperation with pediatricians Donald A. Cornely and Joseph A. Ritter. James Roth and other gastroenterologists studied the local erosion effect of aspirin's hydrolyzing in the stomach to acetic acid and salicylic acid—and demonstrated it in vivo to the marketing executives! The pharmaceutical development department, headed by Albert Mattocks, prepared a special solvent system for the elixir that kept the active ingredient in solution but was low in alcohol and palatable to young patients. The marketing group then proceeded with plans to introduce Elixir Tylenol, using the slogan "for little hotheads" in the caption for the outer carton, which was shaped like a fire engine. Six months after the decision by the New Products Committee to proceed with *N*-acetyl *p*-aminophenol, the U.S. Food and Drug Administration granted its approval, and Elixir Tylenol was introduced in June 1955.

Not long afterward, McNeil Laboratories was purchased by Johnson & Johnson, which had grown since its founding in 1887 into one of the nation's biggest consumer and health-products companies. As part of Johnson & Johnson, McNeil Labs developed and gained FDA approval for a line of Tylenol with codeine, which eventually became the most frequently prescribed of any pharmaceutical brand, followed by other dosage forms and combinations of Tylenol for sale to hospitals and over the counter in drugstores.