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Smoking

by David Holzman

Each puff on a cigarette sends the temperature of the glowing tip soaring to 1800 °F (980 °C). This sets off reactions that produce an estimated 4000 chemicals. A host of carcinogens spew forth, along with poisons, mutagens, and mind-altering drugs.

Raw tobacco contains thousands of chemicals. Cigarette manufacturers add other chemicals to enhance the aroma, flavor, and burning rate. "When you light up, it's like exposing your whole body to a miniature chemical factory," says John Holbrook of the University of Utah Medical Center. Thousands of new compounds are formed in the heat of the flame.

Within seconds, many of these chemicals invade the blood and circulate through the body. They cut down the flow of oxygen to the heart while they force it to pump harder. They sear the lungs and settle in the kidneys and bladder, causing cellular changes that can eventually lead to cancer. They also head straight for the brain, producing either alertness or calm at the will of the smoker.

The allure of nicotine

Researchers pass cigarette smoke through a filter made of glass fibers, separating it into the gas phase and "tar." The tar consists of solid particles and vapors that condense to liquid as they contact the cooler filter. Next, researchers separate and identify some of the compounds in the gas and the "tar" and try to discern what effects they have on the body.

The best-known of these compounds is nicotine, which causes or contributes to most of smoking's physical and mental impact. "Nicotine has all the key addictive properties of cocaine, morphine, and alcohol,

which are our reference standards," says Jack Henningsfield of the National Institute on Drug Abuse Addiction Research Center.

Low doses of nicotine from shallow inhalation stimulate secretions from the adrenal gland, increasing alertness; high doses from deep drags release beta-endorphins, "the body's natural morphine," says Ovide Pomerleau of the University of Connecticut Medical School. The kicker, he adds, is that it acts so quickly. "Twenty-five percent of the nicotine in inhaled smoke goes to the brain within seven seconds. It's well known from psychological research that the immediacy of delivery is very powerful in controlling behavior."

Pomerleau has found that smokers under stress will smoke more, presumably to get the calming influence of the beta-endorphins. Beta-endorphins flow naturally during the body's fight-or-flight response to sudden threats or stress. "Unfortunately," says Pomerleau, "modern life does not give us these outlets. In a highly stressful situation, smoking may reduce some of the anxiety and make a person feel more composed. We have demonstrated nicotine's ability to relieve both pain and anxiety."

Chemical imposter

Nicotine interacts with the nervous system, but another chemical in the smoke, carbon monoxide, poisons the blood. Think of the circulatory system as a subway; each hemoglobin molecule in blood is a subway car with four seats, or binding sites, for oxygen. A delicately balanced, weak attraction between oxygen and the binding sites pulls oxygen into the blood from the oxygen-rich lungs and releases it to oxygen-poor tissues as the blood travels through the body (see "Pumping Oxygen," *Chem Matters*, February 1984).

Carbon monoxide "steals the seat"—occupies the oxygen-binding sites—and hangs onto them with more than 200 times the strength of oxygen. "Heavy smokers have up to 12-14% of their hemoglobin tied up with carbon monoxide," says Dietrich Hoffmann of the American Health Foundation. The body responds by increasing the flow of blood, but the smoker's physical strength and endurance are reduced.

Smoker's cyanide cough

Hydrogen cyanide, HCN, is one of the thousands of compounds produced by burning tobacco. HCN is a potent cellular poison and is famous as the gas used in the gas chamber.

The lungs respond to the buildup of tar by accelerating their normal house-cleaning mechanism. They secrete mucus to trap dirt and tar, then sweep the mucus from the lungs by the action of hairlike cilia. Smoke causes the mucous glands of the lung to work overtime. At the

same time, the hydrogen cyanide in the smoke kills the cilia, and the mucus accumulates. The result is chronic bronchitis—a persistent cough caused by irritation of the windpipe and the buildup of mucus.

Oxidation

In addition to nicotine and carbon monoxide, burning tobacco produces a host of less familiar chemicals, including a large number of substances called oxidants. Oxidants are chemicals that can accept electrons from other chemicals. The classic example is oxygen—the element that lends its name to the phenomenon. The outer shell of an oxygen atom holds six outer electrons, though it has room for eight. In the presence of another chemical, it may “steal” two electrons, thereby completing its own shell and “oxidizing” the other chemical. If the other chemical was using those electrons to hold it together, it would fall apart. Most of the oxidants in cigarette smoke are not ordinary atoms or molecules, but “free radicals” (see side bar, Free radicals).

Because oxidants are all around us, even in fruits and vegetables, the body has evolved detoxifying agents and repair mechanisms. But nothing in nature is as bad for health as the concentration and variety of oxidants in cigarette smoke. A day’s worth of smoking is roughly equivalent to a year’s smog in Los Angeles. “We have come to view cigarette smoke as a super-rich smog,” says William A. Pryor, director of the Program in Free Radical Biology at Louisiana State University.

Roll-your-own smoke

Pryor made a model of cigarette smoke by mixing air; nitric oxide, NO; and a carbon compound called isoprene at the concentrations found in cigarette smoke. The relatively stable nitric oxide slowly oxidizes to produce highly reactive nitrogen dioxide, NO₂. This then reacts with isoprene to produce radicals. Further reactions take place, keeping the concentration of radicals so high that Pryor says, “It would seem incredible to believe that these radicals [in cigarette smoke] are not doing some damage.”

Emphysema

William Pryor’s research has supplied some of the missing pieces in the explanation of how smoking causes emphysema. Emphysema is smoking’s most painful affliction. “You feel as though you are close to suffocation. Eventually you get to the point of talking less because of the need to breathe,” says Edward Brown, an emphysema sufferer who is a former board member of the D.C. Lung Association. Ironically, emphysema may be caused by the body’s own defenses, which are thought to destroy the lung while trying to clear it of tar.

A healthy lung looks like a sponge. With each breath, millions of microscopic balloon-like sacs called *alveoli* fill with air; oxygen in the air passes through capillaries in the alveolar membrane and enters the blood. The alveoli must be very thin to pass oxygen and very elastic so they can expand and contract with each breath. The alveolar membrane is strengthened by strands of a tough, elastic protein called *elastin*. This rubber bandlike material is present in other parts of the body that must stretch, such as ligaments and blood vessels. But the body must be able to destroy elastin to remove tissue damaged by injury or infection. A variety of white blood cells called neutrophils contain *elastase*, an enzyme that can digest elastin. The neutrophils also use elastin to attack and digest foreign bacteria. The body protects itself against the destructive action of elastase by an inhibitor compound secreted by the liver called *α1proteinase inhibitor* (α 1PI). This inhibitor seems to be dramatically affected by cigarette smoke.

In the laboratory, Pryor bubbled fresh cigarette smoke through a buffer solution containing α 1PI. The protective molecule was destroyed, he said, “in a matter of seconds.” This leads to a likely scenario for major lung damage: Tar in the smoke condenses onto the alveolar membrane; this foreign substance mobilizes defense cells, including neutrophils. The neutrophils attack the foreign substance by releasing elastase. The elastin fibers of the lung—normally protected by α 1PI—are vulnerable to this enzyme. In a counterattack gone awry, the lung begins to digest itself. Eventually the alveoli are destroyed, leaving the lung pocked with craters that in extreme cases measure several inches.

It is yet to be proven that smoke destroys α 1PI in the body as it does in the test tube. However, scientists have noted the similarity of emphysema to a rare genetic disorder in which the lungs degenerate. Its sufferers lack α 1PI.

Cancer and denial

For some decades, it has been known that cigarette smoking causes lung cancer and other diseases, including emphysema. The evidence came from some 40,000 studies, including autopsies and population studies. Throughout, the cigarette manufacturers have claimed that the cause-and-effect relationship has never been proven...that the evidence was circumstantial. Now, however, researchers are closing in on the chemical details of just how smoking causes emphysema and some types of cancer. The tobacco companies stand alone in their refusal to acknowledge the health hazards of smoking. Their claims, as *The New York Times* put it 18 years ago, have “the hollowness of a cough in a graveyard.”

SIDE BARS

Free radicals: The smoking gun

Most molecules contain an even number of electrons due to the nature of their bonds. Neighboring atoms within a molecule are typically joined by a covalent bond—a pair of electrons in which both atoms have an interest. In the water molecule below, for example, the hydrogens are attached to oxygen by the shaded electron pairs.

A *free radical* is an atom or molecule with an *unpaired* outer electron, as in NO, nitric oxide. The unpaired electron is shown in color. In the diagram at left, each bonding pair of electrons is represented by a straight line.

Because electrons tend to associate with each other in pairs, a free radical may attack the first molecule it encounters to pair up its odd electron. The free radical may steal an electron, thus converting itself to a stable “even” molecule, or it may attach to the other molecule. Either way, the molecule that is preyed upon is transformed into a free radical. In this fashion, radicals often start chain reactions. Some free radicals are so reactive that they have lifetimes of only 10^{-9} second; others may last for days or years.

A glowing cigarette produces nitric oxide from nitrates in the tobacco. The NO reacts with oxygen to form another “odd” molecule, NO₂, nitrogen dioxide, which in turn attacks other molecules. In this example it attacks *isoprene*, one of the most abundant compounds in cigarette smoke.

Free radicals like those shown can attack polyunsaturated fatty acids, such as the molecule shown below, which are components of cell membranes.

The fatty acids are converted to reactive free radicals, which can combine with oxygen. They may ultimately be degraded to small molecules such as *malondialdehyde*, below, leaving the cell membrane damaged.

William A. Pryor, a researcher at Louisiana State University, uncovered some of these free radical chain reactions. Pryor reported, “The radicals that we detected in gas-phase cigarette smoke are sufficiently reactive to explain some of the known biological effects of smoke.” Pryor’s measurements indicate that gasphase cigarette smoke contains about 5×10^{14} free radicals per puff.

The term “radical” has several meanings in chemistry. It is sometimes used to denote stable charged groups of atoms with even numbers of electrons such as SO₄²⁻ and CO₃²⁻. Some authorities call these groups

“polyatomic ions” to minimize confusion. In this article, the term “free radical” refers only to groups of atoms, charged or neutral, with an unpaired electron.

Cigarette additives

Tobacco is not the only ingredient in cigarettes. When tobacco companies began manufacturing lowtar cigarettes, smokers found them relatively tasteless. The manufacturers responded by adding flavor ingredients. A richer taste is achieved by adding licorice, cocoa, or chocolate; a green-apple taste may come from *cis*-3-hexenyl propionate; an earthy, meaty smell from hexyl-2-furoate. The most common additives are sugar (up to 14% of some cigarettes) and glycerin (keeps tobacco moist). Are these additives safe? Some tobacco companies say they use only FDA-approved food additives. These are safe to eat. However, when burned in the presence of tobacco, the compounds are decomposed, oxidized, and chemically rearranged, forming new compounds whose effects are unknown. Tobacco researchers generally do not encounter these compounds because they use a standard (1R1) cigarette, made at the University of Kentucky, which contains small amounts of glycerin and sugar, but none of the flavor additives.

In 1983, *Mother Jones* magazine said that some tobacco companies add a spice called “deer tongue” to their cigarettes. This herb contains coumarin, a poison that was banned from food by the FDA in the 1950s. Was the magazine report correct? Is this additive still being used? *Chem Matters* wrote to the major tobacco companies and the Tobacco Institute, asking for a list of chemicals added to cigarettes. American Brands (maker of Bensen and Hedges and Carlton) said, “The information you requested is proprietary [a trade secret], and, therefore, cannot be provided.” Other companies simply did not reply. The Tobacco Institute said, “We do not have detailed information.” They did send us a brochure entitled “About Tobacco Smoke...and how little is known about it on a truly scientific basis.” In the same brochure the Tobacco Institute denied that there is any such thing as tar in cigarettes: “We keep hearing about tar...even though there is no tar as such in tobacco smoke! The so-called tar is the particulate matter collected by supercooling and condensing tobacco smoke with special laboratory equipment in a manner far different from the way we smoke cigarettes.”

The brochure failed to point out that the industry’s secrecy is one of the reasons more is not known. In fact, because the identity of additives is a closely guarded secret, smokers have no way of knowing what chemicals are in their cigarettes. In contrast to the extensive regulations

controlling food, cosmetics, and beverages, no government agency regulates the content of cigarettes in any way. (David P. Robson)

Smoking facts

From the Tobacco Institute: In 1984...

- U.S. factories made 668 billion cigarettes.
- average consumption per U.S. citizen was 3454, down from the record of 4345 in 1963.
- Americans spent \$28.7 billion on cigarettes.
- U.S. farmers grew 786,700 metric tons of tobacco; the world leader, China, produced 1,500,000 metric tons.
- about one-third of the sale price of cigarettes went for state and federal taxes.

From the Journal of the American Medical Association: In the United States...

- about 29% of adults smoke.
- 53 million people smoke, but 33 million have stopped.
- of 14 studies of the effects of tobacco smoke on nonsmokers, all but one showed evidence of a higher risk of lung cancer.
- smoking effects are estimated to cost well over \$100 billion per year; most of these costs are borne by nonsmokers.
- each year there are 350,000 “premature deaths” related to smoking. That’s 1000 people per day.
- with current medical knowledge, it is clear that if tobacco were being evaluated by governmental regulatory agencies today for anticipated release to the consumer, it would not be allowed on the market.

CAPTIONS

Because smoking reduces physical prowess, the tobacco industry has been criticized for running advertisements that appeal to athletes. In 1964 the tobacco industry voluntarily agreed that its advertising would not show “as a smoker any person well known as being or having been an athlete” or anyone “participating in, or obviously having just participated in, physical activity requiring stamina or athletic conditioning beyond that of normal recreation.” Also to be suspended were ads suggesting that “smoking is essential to social prominence, distinction, success, or sexual attraction.” Current advertisements appear to violate the industry’s own pledge.

A microscopic section of a normal lung. The open spaces are air sacs that expand and contract with each breath—like a bellows. Each sac is lined with elastic tissue that contains numerous capillaries.

A sample of lung tissue after repeated exposure to tobacco smoke. Some air sacs have ruptured, leaving larger sacs with less elasticity. Oxygen transfer is impeded by reduction of both the tissue surface area and the number of capillaries.

BIOGRAPHY

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REFERENCES

- Cairns, John. "The Treatment of Diseases and the War Against Cancer," *Scientific American* **1985**, 253(5), 51-59.
- Wagner, Susan. *Cigarette Country: Tobacco in American History and Politics*; Praeger: New York, N.Y., 1971.
- Cummins, Ken. "The Cigarette Companies: How They Get Away with Murder," *The Washington Monthly* **1984**, April, 15-24.
- "The Health Consequences of Smoking: Cancer. A Report of the Surgeon General"; U.S. Department of Health and Human Services: Washington, D.C., 1982; (PHS) 82-50179.
- Janoff, Aaron. "Biochemical Links Between Cigarette Smoking and Pulmonary Emphysema," *J. Appl. Physiol.* **1983**, 55(2), 285-93.
- J. Am. Med. Assoc.* **1984**, 252(20) and **1985**, 253(20); much of these two issues was devoted to health effects of smoking.
- Neuberger, M. B. *Smoke Screen: Tobacco and the Public Welfare*; Prentice Hall: Englewood Cliffs, N.J., 1963.
- The New York Times*, Aug. 22, 1967, p. 38.
- Owen, David. "The Cigarette Companies: How They Get Away with Murder, Part II," *The Washington Monthly* **1985**, March, 48-54.
- Pryor, William A. "Oxy-Radicals and Related Species: Their Formation, Lifetimes, and Reactions," *Annu. Rev. Physiol.* **1986**, 49.
- Pryor, William A.; Dooley, Margaret M.; Church, Daniel F. "Mechanisms of Cigarette Smoke Toxicity: The Inactivation of Human α -I-proteinase Inhibitor by Nitric Oxide/Isoprene Mixtures in Air," *Chem.-Biol. Interact.* **1985**, 54, 171-83.
- Pryor, William A.; Tamura, Masamitsu; Church, Daniel F. "ESR Spin-Trapping Study of the Radicals Produced in NO_x/Olefin Reactions: A Mechanism for the Production of the Apparently Long-Lived Radicals in Gas-Phase Cigarette Smoke," *J. Am. Chem. Soc.* **1984**, 106, 5073-79.
- Taylor, Peter. *The Smoke Ring: Tobacco, Money, and Multinational Politics*; Pantheon Books: New York, N.Y., 1984.
- Wynder, E. L.; Hoffman, D. *Tobacco and Tobacco Smoke*; Academic Press: New York, N.Y., 1967.