highly efficient vector, a nonimmune population, and mining conditions that encouraged both vector breeding and malaria transmission fueled recurrent epidemics of malaria, which apparently started in the 1940s or early 1950s; 80% of the cases were *P. falciparum*.

In 1955, public health authorities in Pailin began distributing chloroquine to workers daily; later, the frequency was reduced to twice a week. In 1960, they began administering chloroquine indirectly through medicated salt. This method increased coverage but made it difficult to ensure that each worker consumed an adequate dose of the drug. The repeated application of subcurative concentrations of chloroquine to a highly infected population set the stage for the emergence of chloroquine-resistant strains of *P. falciparum*. The subsequent transmission of resistant strains of falciparum to new waves of nonimmune workers, month after month, and their treatment with high but often noncurative doses of chloroquine amplified resistance. By 1973, 90% of falciparum malaria cases were resistant to chloroquine, and 70% exhibited high levels of resistance.

An audio interview with Dr. Packard is available at NEJM.org

From the Thai–Cambodian border, resistant falciparum malaria spread to surrounding areas along with the returning migrant workers. Secondary patterns of dispersal from these surrounding areas contributed to the wider dissemination of chloroquine resistance throughout South and Southeast Asia.

Mass drug-administration (MDA) programs elsewhere in the world during the 1950s and 1960s may also have contributed to the rise of chloroquine resistance. There is a strong correlation between the geographic areas where MDA programs were initiated and the places where chloroquine resistance first emerged. Also contributing to the development of resistance was the widespread availability of chloroquine in shops and private pharmacies, lax regulation of use of the drug, and the absence of effective primary care systems.

It is not surprising that Pailin was an early site for the emergence of artemisinin resistance. Some observers have suggested that malaria parasites in that region may be particularly prone to mutation. Yet it is clear that although the drugs have changed, the social and economic conditions under which they are used have not. Pailin remains the center of an extensive migrant labor system, with limited health resources. In addition, the widespread availability in the region of cheap counterfeit drugs containing subclinical quantities of artemisinin and the marketing and use of noncombination forms of the drug have created an ideal mix of conditions for both the development and spread of artemisinin resistance.[4]

An intensive campaign is currently under way to eliminate artemisinin resistance in the greater Mekong Delta region and prevent its further spread. These efforts focus on identifying and treating to cure all cases of malaria in the region. Whether these efforts will be successful is unclear. But efforts to address the social and economic conditions that contribute to the spread of malaria and foster antimalarial resistance, including the marketing of monotherapies and counterfeit drugs, are essential steps for preventing artemisinin-based drugs from following the path of chloroquine. Given the cyclical history of drug development followed by the emergence of resistance, it is also critical that investments continue to be made in the development and production of new generations of antimalarial therapies.

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Big Marijuana — Lessons from Big Tobacco

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The United States is divided over the legalization of marijuana. Arguments in favor include protection of individual rights, elimination of criminal sentencing for minor offenses, collection of tax revenue, and elimination of the black market. Counterarguments include the

possible escalation of use, adverse mental and physical health effects, and potential medical and social costs.

Some steps have already been taken to reduce harsh and racially biased sentencing. There is growing support in Congress to eliminate federal mandatory minimums for drug offenses, and 19 states have either decriminalized or eliminated jail time for possession of small amounts of marijuana. Furthermore, 21 states and the District of Columbia have legalized the medical use of marijuana.

Washington State and Colorado went further, authorizing the retail sale of marijuana and opening the door to a legal marijuana industry. Given the lessons learned from the 20th-century rise of another legal addictive substance, tobacco, we believe that such an industry could transform marijuana and its effects on public health. Like tobacco, marijuana harms health and is addictive; unlike alcohol, both tobacco and marijuana came of age after the Industrial Revolution. And although the United States has, since tobacco's rise, adopted regulatory structures designed to protect consumers, they do not apply to marijuana, in part because marijuana use and sales remain illegal under federal law. Colorado and Washington are developing regulatory infrastructures to fill this gap, but the goals and potential effectiveness of their proposed regulations are unclear. No evidence exists regarding which regulations might minimize population harm from marijuana. The marijuana industry's trajectory could therefore repeat tobacco's.

In its current form, smoked marijuana is less deadly than tobacco. Although case–control studies have found increased mortality associated with heavy marijuana use — attributable to vehicle crashes from driving while high, suicide, respiratory cancers, and brain cancers[1] — the nonfatal adverse effects of marijuana use are much more prevalent. These include respiratory damage, cardiovascular disease, impaired cognitive development, and mental illness. These harms are very real, though they pale in comparison with those of tobacco, which causes almost 500,000 U.S. deaths annually. Marijuana is also less addictive than tobacco. About 9% of cannabis users meet the criteria for dependence (according to the *Diagnostic and Statistical Manual of Mental Disorders*) at some time in their lives, as compared with 32% of tobacco users.[2]

But tobacco was not always as lethal or addictive as it is today. In the 1880s, few people used tobacco products, only 1% of tobacco was consumed in the form of manufactured cigarettes,[3] and few deaths were attributed to tobacco use. By the 1950s, nearly half the population used tobacco, and 80% of tobacco use entailed cigarette smoking; several decades later, lung cancer became the top cause of cancer-related deaths.[3] This transformation was achieved through tobacco-industry innovations in product development, marketing, and lobbying.

The deadliness of modern-day tobacco stems from product developments of the early 1900s. Milder tobacco blends and new curing processes enabled smokers to inhale more deeply, facilitated absorption by lung epithelia, and boosted delivery of nicotine to the brain. Synergistically, these changes enhanced tobacco's addictive potential and increased intake of toxins. In addition, the industry added other ingredients, including toxic substances that enhanced taste and sped absorption — without regard for safety. When tobacco was a cottage industry, cigarettes were either "roll-your-own" or expensive hand-rolled products with limited market reach; after industrialization, machines rolled as many as 120,000 low-cost, perfectly packaged cylinders daily.

The burgeoning marijuana industry is already following the same successful business strategy by increasing potency and creating new delivery devices. The concentration of tetrahydrocannabinol (THC), marijuana's principal psychoactive constituent, has more than doubled over the past 40 years.[4] Producers are manufacturing strains that they claim are less addictive or less harmful to mental health, but no supporting scientific evidence has been published. New vaporizer delivery systems developed by some manufacturers may reduce lung irritation from smoking but may also allow users to consume more THC (the component most closely associated with euphoria, addictive potential, and mental health side effects) by enabling them to inhale more often and more deeply. The business community recognizes these innovations' economic potential: a recent joint venture between a medical-marijuana provider and an electronic-cigarette maker sent stock prices soaring.

Marketing strategies go hand in hand with product innovation. The market for marijuana is currently small, amounting to 7% of Americans 12 years of age or older, just as the tobacco market was small in the early 20th century. Once machines began mass-producing cigarettes, marketing

campaigns targeted women, children, and vulnerable groups by associating smoking with images of freedom, sex appeal, cartoon characters, and — in the early days — health benefits.

There is reasonable evidence that marijuana reduces nausea and vomiting during cancer treatment, reverses AIDS-related wasting, and holds promise as an antispasmodic and analgesic agent.[5] However, marijuana manufacturers and advocates are attributing numerous other health benefits to marijuana use — for example, effectiveness against anxiety — with no supporting evidence.

Furthermore, the marijuana industry will have unprecedented opportunities for marketing on the Internet, where regulation is minimal and third-party tracking and direct-to-consumer marketing have become extremely lucrative. When applied to a harmful, addictive commodity, these marketing innovations could be disastrous. This strategy poses a particular threat to young people. Adolescents are more likely than adults to seek novelty and try new products. The developing adolescent brain is particularly vulnerable to the development of addiction. According to the Substance Abuse and Mental Health Services Administration (SAMHSA), children who use marijuana are up to four times as likely as adults to become chronic, heavy users — the type that would generate consistent sales for the marijuana industry.

Today, nearly one in five U.S. adults still smokes, despite extensive public health campaigns focused on reducing uptake and increasing cessation. The tobacco industry has provided a detailed road map for marijuana: deny addiction potential, downplay known adverse health effects, create as large a market as possible as quickly as possible, and protect that market through lobbying, campaign contributions, and other advocacy efforts.

The tobacco industry, bolstered by enormous profits, successfully lobbied to be exempted from every major piece of consumer-protection legislation even after the deadly consequences of tobacco were established. With nothing to sell or profit from, health advocates had difficulty fighting a battle that was clearly in the best interest of the public. The marijuana industry has already formed its own advocacy organization — the National Cannabis Industry Association — to protect and advance its corporate interests.

It took the medical and public health communities 50 years, millions of lives, and billions of dollars to identify the wake of illness and death left by legal, industrialized cigarettes. The free-market approach to tobacco clearly failed to protect the public's welfare and the common good: in spite of recent federal regulation, tobacco use remains the leading cause of death in the United States.

Addictive substances with known harms may merit completely new policy approaches. For example, the government of Uruguay's marijuana program will restrict sales to government-produced strains, limit prices in order to undercut illicit markets, and closely monitor individual consumption. The effects and side effects of this approach, however, remain to be seen. At present, we should accelerate collaboration among the Food and Drug Administration, the National Institutes of Health, SAMHSA, the National Highway Traffic Safety Administration, and other agencies to fully understand current harms and forecast the effects of industrialization.

In theory, any revenues from sales of marijuana products should pay for all regulation and harms so that society will not have to pick up the tab for damage done by the product. However, we know from the history of tobacco that this is hard to implement in practice.

History and current evidence suggest that simply legalizing marijuana, and giving free rein to the resulting industry, is not the answer. To do so would be to once again entrust private industry with safeguarding the health of the public — a role that it is not designed to handle.

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