Modern electronic cigarettes (e-cigarettes) were first introduced to the international market in 2007 and were lauded as a tool for smoking cessation (1, 2). Little known, however, is that the origin of the modern e-cigarette traces back to the 1960s, at a time when the tobacco industry was grappling with newfound knowledge of the carcinogenic effects of smoking. Under the codename Project Ariel, a group of scientists for the British American Tobacco company sought to develop a novel, aerosol-based device to deliver nicotine while avoiding or diminishing the detrimental effects of cigarette smoke. After three years in development, a device was patented but was never brought to market; rather, British American Tobacco hid Ariel because of the threat it posed to cigarettes, which at the time seemed invulnerable to regulation (3). But in 2003, the Chinese pharmacist Hon Liu developed and marketed the first modern e-cigarette, designed to look similar to a conventional tobacco cigarette.

Modern e-cigarettes have rapidly undergone four “generations” of evolution, starting with the first-generation “cig-a-like” disposable e-cigarettes. The second-generation e-cigarettes (commonly called vape pens) were designed to look significantly different from conventional tobacco cigarettes, with larger sizes and multiple colors, and had the added function of refillable cartridges and tanks with rechargeable batteries. Third-generation devices, also called “tank” or “mods,” allowed further customization with adjustable voltage, temperature, and atomizer resistance. The latest generation, known as “pod” devices, with common brands including JUUL (JUUL Labs), FLUM (Flumigo Technology Limited), and Suorin (Suorin), differ most notably from prior devices to nonsmokers, particularly children and young adults. Although first-generation e-cigarettes were available only in tobacco flavors, the e-cigarette industry rapidly expanded to fruity, minty, coffee, dessert, and even cocktail flavors. This flavor explosion increased the appeal of these nicotine delivery devices to nonsmokers, particularly children and young adults (5). Although the expansion of flavors was a wise business move by the tobacco industry to expand the population of e-cigarette users by targeting individuals across our diverse population, the addition of thousands of chemicals to e-liquids to create different flavor profiles has led to challenges in defining the health risks of these inhalants.

The U.S. Food and Drug Administration (FDA) recently made significant strides to remove nontobacco flavors from the e-cigarette industry through the restrictions introduced in the September 2022 rule. These safeguards are underpinned by a decade of growing evidence on the adverse health effects of e-cigarettes and have been supported by the American Thoracic Society (6–8), among others. The U.S. Food and Drug Administration (FDA) recently made significant strides to remove nontobacco flavors from the e-cigarette industry through the restrictions introduced in the September 2022 rule. These safeguards are underpinned by a decade of growing evidence on the adverse health effects of e-cigarettes and have been supported by the American Thoracic Society (6–8), among others.

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market, in parallel with removing menthol-flavored tobacco products from the market. Furthermore, the FDA recently began implementing regulation of all e-cigarettes, whether they contain regular or synthetic nicotine, with the goal of approving the applications of only those e-devices that can be shown to be both nontoxic and not appealing to children and young adults. In June 2022, the FDA issued marketing denial orders to Juul Labs Inc., a giant in the industry (6, 7). Although these rulings are significant, many types of e-cigarettes remain on the market. Furthermore, many flavored e-cigarettes and e-liquids are made outside the United States and are easily ordered online for shipping directly to consumers’ doors, such that the consumption of flavored e-cigarettes will continue. Of direct importance to the paper by Hickman and colleagues (pp. 1248–1258) in this issue of the Journal (8), the vast majority of published literature on e-cigarettes to date relates to earlier generation e-devices and lacks direct generation-to-generation comparisons. Thus, very little is known about the differential health effects of using one generation of e-cigarette over another.

Hickman and colleagues (8) evaluate the impact of e-cigarette use on immune homeostasis in the respiratory tract through examination of soluble mediators in sputum. Unique to this study is a design that analyzes third- and fourth-generation e-cigarette users in separate groups. Induced sputum was collected from four groups: nonsmokers/nonvapers, combustible tobacco smokers, third-generation e-cigarette users, and fourth-generation e-cigarette users. The primary endpoint was differences in 45 soluble mediators associated with inflammation, host defense, and lung injury in sputum supernatant. Of 45 mediators evaluated, 12 had significant differences among groups. The authors found overall reduced concentrations of mediators in fourth-generation e-cigarette users, and they specifically highlight lower concentrations of sILCAM-1 (soluble intercellular adhesion molecule-1) and sVCAM-1 (soluble vascular cell adhesion molecule-1) in fourth-generation e-cigarette users relative to nonsmokers/nonvapers and third-generation e-cigarette users. The authors suggest that these differences may indicate an overall suppression of host defense associated with fourth-generation e-cigarette use, and they hypothesize that this may be attributable to the inhalation of high concentrations of nicotinic salts (8).

This study adds to the current body of literature that demonstrates significant alterations to the inflammatory and immune milieu associated with long-term e-cigarette use. In one study by Ghosh and colleagues, combustible tobacco and e-cigarette smokers were found to have higher concentrations of proteases, including neutrophil elastase, matrix metalloproteinase-2, and matrix metalloproteinase-9, in BAL samples compared with nonsmokers/nonvapers, without a concomitant increase in antiprotease concentrations (9). Sayed and colleagues compared sputum and saliva from nonsmokers/nonvapers with those of e-cigarette users and found a reduction in markers of airway inflammation in vapers. Interestingly, the investigators also examined plasma in both groups and found higher circulating concentrations of certain inflammatory cytokines, chemokines, and growth factors in e-cigarette users, in particular TNF-β (tumor necrosis factor-β) and VEGF (vascular endothelial growth factor), suggesting that changes in airway inflammatory markers may represent a counter-response to general inflammation caused by chronic e-cigarette use (10). Reidel and colleagues evaluated induced sputum samples from combustible tobacco smokers, e-cigarette users, and nonsmokers/nonvapers and found elevated markers of neutrophil activation in e-cigarette users without an increase in absolute neutrophil number, suggesting an imbalance of innate immune defense in e-cigarette users (11). And although the findings of Corriden and colleagues were not identical to those of Reidel and colleagues, they identified decreased neutrophil functional abilities in the circulation of e-cigarette users, confirming negative effects of vaping on innate immunity (12).

Limitations of Hickman and colleagues’ study include overrepresentation of male subjects within the fourth-generation e-cigarette group, which the authors controlled for in their analysis. Beyond classifying e-cigarette users by generation of device, the e-cigarette groups were not further characterized regarding flavor, frequency, or chronicity of use or concomitant use of marijuana-containing products (8). This limitation highlights a challenge for the tobacco research community at large to develop high-quality, common survey instruments to accurately quantify concomitant combustible tobacco and marijuana use, as well as types, flavors, and frequency of e-cigarettes and e-liquids used. The University of California, San Diego, has developed an inhalant use survey (freely available on Redcap) (13, 14), but even that instrument must be updated every 6–12 months because of the rapid evolution of the e-cigarette market.

Overall, the study by Hickman and colleagues is the first to differentiate the effects of e-cigarette use on the basis of generation of e-device. The highlighted differences between third- and fourth-generation e-cigarettes in their study suggest that prior published data generated from first- through third-generation e-devices may not apply to the most current e-cigarette users, who primarily use fourth-generation devices. Specifically, the immunologic and pathologic consequences related to e-cigarette use differ depending on e-device and e-liquid. Further studies are needed to determine what other e-cigarette factors are affecting lung and systemic health, such as flavorants, composition of pods and tanks, and puff topography (Figure 1). Finally, in this era of multiinhalant use when many e-cigarette vapers also smoke conventional tobacco (dual use) and/or use marijuana (smoke or vape), it is critical that we undertake studies

Figure 1. Multiple factors affect the chemical composition of the e-cigarette aerosols generated during vaping, and multiple factors influence the effects on the human body.
to understand how these inhalants may interact to cause new or more severe effects on human health (Figure 1).

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Idiopathic Pulmonary Fibrosis Genetic Risk Factors, Function, and Mechanisms? The Concepts Are Starting to Gel

Patients with pulmonary fibrosis are more likely to carry certain alleles, including variants for the genes MUC5B (mucin 5B) (1) and DSP (desmoplakin) (2). However, in a world where 10% of the general population also carries these alleles, which at-risk carriers

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