Another consideration in dosing this TTDN is the achieved physiological effect. Although this trial protocol used a standard predetermined target electrical output from the pacing device for all patients, the degree of phrenic nerve stimulation, and thereby the potential to increase force of diaphragm contraction, also depends on the relative stimulation threshold. This is impacted by the distance between the selected electrode and the nerve, in addition to the resistance posed by the tissues, both of which may vary significantly between individuals. Comparing and standardizing dosing is therefore difficult based on TTDN settings alone without assessment of the effect on individual patient mechanics.

In summary, diaphragm dysfunction is a common and clinically important problem in need of a solution. TTDN appears safe and largely feasible and has shown a physiological signal of benefit in this latest study. Despite this, there is further work to be done to establish the optimal treatment dosing, timing of initiation, and target population. We look forward to following further developments in this field. ■

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How Differential Are the Effects of Smoking Cannabis versus Tobacco on Lung Function?

Cannabis use has increased in recent years with the decriminalization of its production and medicinal or recreational use. Because of the similarity in smoke contents between cannabis and tobacco (1), there is a nagging concern that smoking cannabis might have deleterious effects on lung function, similar to the well-known consequences of tobacco smoking. However, the relatively sparse literature involving systematic examinations of the impact of cannabis use on lung function suggests little independent effect of cannabis on FEV_1 (2–9) and an actual increase in FVC and other measures of lung volume (7–9). These results are in contrast to the clearly detrimental effect of tobacco on FEV_1 with little or no effect on FVC in otherwise healthy

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individuals. Studies of the relationship between cannabis and small airway function have been mixed, one showing no effect on multiple measures of peripheral airways function (3) and another showing a decrease in maximal mid-expiratory flow (forced expiratory flow $[FEF]_{25–75\%}$) (2). Moreover, the few studies that have examined the effect of cannabis on specific airway conductance (sGaw) have uniformly demonstrated a modest decrease (3–7), implying a detrimental effect on central airways of uncertain clinical significance, but consistent with histologic evidence of pathology similar to that found in tobacco smokers in bronchial biopsies (10). The few reported longitudinal studies of the effect of cannabis on lung function have yielded mixed results, some not showing any impact on lung function decline (7, 11) and others suggesting an acceleration in the trajectory of FEV_1 decline compared with control nonusers over periods of several to 20 years (12, 13), although the latter effects were mainly confined to those with heavy lifetime use of cannabis (20 or more joint-years, i.e., number of joints/day times number of years cannabis was regularly smoked). It is also noteworthy that most published studies to date have mainly included young adults despite recognition that the deleterious effects of tobacco on lung function may not become detectable until later in life. In view of the latter issue and the mixed results in the literature, the study of the effects of cannabis on lung function in mid–adult life reported by Hancox and colleagues in this issue of the *Journal* (pp. 1179–1185) is of particular interest (14).

Hancox and colleagues report the results of an extensive battery of lung function measurements at age 45 years in the Dunedin (New Zealand) cohort they have followed since birth with a principal focus on the relationship between self-reported cannabis use (adjusted for concomitant tobacco use) and pulmonary function. The importance of this cohort study is accentuated by the fact that most studies of the impact of cannabis use on lung health have been largely limited to younger users. Among 45-year-old participants in the current study, findings in association with cannabis use, adjusted for sex, height, weight, and tobacco use in pack-years, are largely similar to those reported previously in the same birth cohort at age 32: higher FVC (or trend thereto), normal FEV_1 but lower FEV_1/FVC (attributable to the trend toward an increased FVC), higher TLC, FRC, residual volume and V_A, and lower sGaw (7).

A major exception was a significantly lower $FEF_{25–75}$ at age 45 ($n = 881$) that was not reported in the same cohort at age 32 ($n = 919$). This finding accords with the significantly reduced maximal expiratory flow rates at 50% and 75% of forced expired volume reported in association with cannabis in an earlier population-based study (2) but conflicts with the findings of no significant effect of cannabis use on several measures of peripheral airways function in a convenience sample of heavy habitual smokers (3). However, because participants in these latter studies were mainly younger adults, the effect of cannabis smoking on lung function in older individuals could not be adequately assessed.

The finding of a significantly reduced $FEF_{25–75}$ in independent association with cannabis in the present study (14) suggests that the differential effects between tobacco and cannabis smoking might be confined mainly to the disparate effects on FVC, which might be attributable not to any intrinsic effect of cannabis smoke but rather to the unique smoking topography characteristic of cannabis smokers, who usually take deeper inhalations with a much longer breath-holding time and larger inspiratory volume compared with the typical profile of tobacco smoking (15). The characteristic smoking profile of cannabis smokers appears to be analogous to the deep inhalations and long breath-holds of competitive swimmers, who have been shown to have higher than normal lung volumes (16). In addition to the effect on $FEF_{25–75}$, another similarity between the effects of cannabis and those of tobacco on lung function is the qualitatively similar effects on sGaw, as shown in the current and previous studies (3, 6, 7).

An important finding in the current study is a significantly lower transfer capacity of the lung for the uptake of carbon monoxide (T_{LCO}) and T_{LCO}/V_A in cannabis smokers among current or ex-tobacco smokers with adjustment for tobacco pack-years. Nevertheless, the T_{LCO} was not reduced in approximately half of the cohort who never smoked tobacco, possibly implying an additive effect of cannabis and tobacco on this outcome. However, if cannabis were indeed associated with a reduced D_{LCO} in mid–adult life, it would be another example of a qualitative similarity to a tobacco effect. A reduced D_{LCO} could imply a possible relationship to early emphysema, although no independent relationship of self-reported cannabis use to macroscopic emphysema on thoracic computed tomographyscans has been found (6, 17). On the other hand, several case series have reported an association of cannabis with bullous lung disease (18). Clearly, further studies are needed to confirm the relationship between cannabis and diffusion impairment and examine its clinical implications.

It is further noteworthy that cannabis smokers in the current study were mostly light smokers (fewer than 5 joint-years), consistent with the general observation that cannabis is usually smoked in a much lower quantity compared with tobacco. Because a significant impact of cannabis on FEV_1 has been found previously, mostly in heavy smokers of 20 or more joint-years (9, 12, 13), future studies should include larger numbers of heavy cannabis smokers with lung function assessed at later stages of life. ■

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Mesenchymal Stromal Cell Extracellular Vesicles: A New Approach for Preventing Bronchopulmonary Dysplasia?

Bronchopulmonary dysplasia (BPD) is the most common complication of prematurity, affecting about one-third of infants born less than 1.5 kg and less than 29 weeks gestational age (1). BPD is characterized by abnormal bronchial and bronchiolar mucosal metaplasia and hyperplasia, decreased number of alveoli, and abnormal vascular organization, leading to a chronic disease that affects the lung parenchyma, pulmonary circulation, and brain development.

Lung formation begins between weeks 3 and 6 of gestation, but the maturation of peripheral lung saccules into mature alveoli does not occur until the last trimester (28–40 wk). Thus, preterm infants are often forced to breathe at a time before alveolar differentiation and vascularization are complete. Lacking sufficient respiratory capacity, many premature infants are subjected to recurrent lung injury from the high concentrations of supplemental oxygen and mechanical ventilation that are needed to keep them alive. Although most infants with BDP survive, the majority are left with a chronic lung disease characterized by decreased alveolarization, cystic emphysema, fibrosis, and pulmonary vascular remodeling (2). Pulmonary hypertension develops in nearly 60% of severe BPD infants by Day 7, and its presence beyond 3 months is associated with mortality rates of 40–50% (3). Neurocognitive development is also impaired in BPD, likely due to prematurity, hypoxia, and systemic inflammation, leading to a greater frequency of cerebral palsy, intellectual disability, and reduced intelligence quotient scores in very-low birth weight infants who develop BPD than in those who do not (4).

Inflammation induced by pneumonia, systemic nosocomial infection, and barotrauma plays a major pathogenic role. Concentrations of neutrophils and macrophages that produce proteases, reactive oxygen species, and inflammatory cytokines, including IL-1β, IL-6, and IL-8, are elevated in tracheal aspirates of BPD infants (5). Interestingly, infants with respiratory distress syndrome who progress to BPD exhibit persistently elevated concentrations of inflammatory cells and cytokines, whereas those who do not develop BPD show a marked decrease within the first 1–2 weeks (5).

Despite major advances in perinatal care, no specific therapies for BPD have been found to be effective, and treatment is directed at minimizing further lung damage and supporting normal lung development. Advancing treatment of BPD will require therapies that combat both the arrested development and persistent inflammation that occurs. One such approach has been the use of mesenchymal stem cells (MSCs). These pluripotent cells typically transform into osteoblasts, adipocytes, and chondroblasts *in vitro*. However, their limited ability to differentiate into nonmesodermal cells *in vivo* challenges their identity as true stem cells; thus, the more current term is mesenchymal stromal cells. MSCs have been shown to differentiate into surfactant-producing epithelial cells both *in vitro* and after injection into live animals (6). In addition to their

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