of patients with CF. The fact that the inhibition or the genetic ablation of genes controlling sphingolipid synthesis have been associated with hepatic steatosis suggests that the long-term effects of sphingolipid metabolic deficiencies may become associated with excessive hepatic triglyceride accumulation (16).

How are CFTR mutations linked to deficient sphingomyelin hydrolysis, accumulated ceramide, deficient acid ceramidase, and decreased sphingosine? Answers to this question may provide important information about the essential role of sphingomyelin metabolism in cell membrane function in CF. Furthermore, the impact of lipid accumulation may pose an important insight into CFTR pathophysiology beyond that which is addressed by current modulator therapy, contributing to therapeutic outcomes. Gardner uses innovative technology to explore the role of sphingomyelin, ceramide accumulation, and deficient sphingosine production in cellular function and pathophysiology in CF. The use of recombinant acid ceramidase as a potential antiinflammatory therapeutic makes sense from a basic biological standpoint, associating the intricacies of cellular design and the impact of deficient CFTR on cell function. The answer lies in the details of understanding CFTR mechanistically beyond ion transport in the hunt for management of all of the disease-associated pathologies for individuals who suffer from CF. ■

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Revisiting the Role for HIF Stabilizers in Bronchopulmonary Dysplasia

Bronchopulmonary dysplasia (BPD), a form of chronic lung disease, is a severe complication for newborns born prematurely, particularly for those born at extremely low gestational ages. The physiopathology of BPD remains incompletely understood but can be summarized by the consequence of various perinatal injuries, such as infection, mechanical ventilation, and oxygen therapy, on a predisposing field: the immature lung (1). At the histological level, BPD is primarily characterized by airspace enlargement due to defective alveolar formation, a process tightly regulated by a complex and mutually dependent relationship among pulmonary epithelial, interstitial, and endothelial cells (2). Although the past decade has allowed for improved survival of infants with extremely low gestational age, owing to antenatal glucocorticoid treatment, surfactant therapy, and less injurious neonatal resuscitation strategies, the incidence of BPD has not been reduced, and BPD, often complicated by pulmonary hypertension (PH), continues to be a major challenge for neonatologists and pediatricians. The identification of new actionable targets to prevent and treat BPD is thus a major research priority, and this is especially true as a growing body of research evidence is now available describing survivors of BPD as a population exhibiting poor neurodevelopmental outcomes

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together with persistent pulmonary sequelae, thus making them more susceptible to develop a variety of adult chronic lung diseases, including chronic obstructive pulmonary disease and adult PH (1, 2).

Given the multifactorial etiology of the disease, multiple preclinical animal models have been generated and continue to be optimized with the aim to better reflect the etiological complexity of BPD, understand the pathophysiological mechanisms, and test therapeutic options. Over the past 20 years, elegant studies have revealed the absolute requirement of the HIFs (hypoxia inducible 2 factors) and/or VEGF (vascular endothelial growth factor) and/or VEGF receptor signaling for microvascular lung development and associated alveolarization (3–5). In agreement with this, disruption of this signaling pathway has been documented as a common feature of animal models of BPD (1), pushing different groups to investigate whether forced activation of HIFs or their downstream targets offer therapeutic benefits. Concordant results were obtained showing that stimulation of HIF transcriptional activity secondary to inhibition of PHDs (prolyl hydroxylase domain-containing proteins) or gene therapy preserves alveolar growth in neonatal rats and preterm baboons exposed to hyperoxia (5, 6).

In this issue of the *Journal*, Hirsch and colleagues (pp. 1146–1158) provide additional preclinical evidence underscoring the therapeutic efficacy of HIF stabilization in attenuation and prevention of BPD (7). By combining intraamniotic injection of *Escherichia coli* endotoxin (mimicking human chorioamnionitis) and preterm delivery, the authors sought to determine whether prenatal stressors are sufficient to compromise alveolar development in the offspring and whether this anticipated defect could be rescue by activation of HIFs. As anticipated, reduced expression of HIF-1α and HIF-2α and their target genes (VEGF and endothelial nitric oxide synthase) decreased pulmonary vascular density, increased airspace enlargement, and increased right ventricular hypertrophy (RVH) were noticed in 14-day-old pups maternally exposed to endotoxin. Remarkably, all of these abnormalities were partially or completely cancelled on antenatal or postnatal inhibition of PHDs with dimethyloxalylglycine or GSK360A, reinforcing the notion that downregulation of HIF expression is a causal factor of impaired microvascular and alveolar growth, irrespective of the nature and timing of the insult. In direct connection with this topic, the same group also demonstrated that postnatal supplementation in IGF-1 (insulin-like growth factor 1) and its binding protein IGFBP-3, a PHD-independent positive regulator of HIF-1α expression, significantly preserves lung structure and function and prevents RVH in three different animal models of BPD, including intraamniotic injection of endotoxin (8). These findings validate promising results of a phase 2 randomized controlled trial (NCT 01096784) reporting a decrease in the occurrence of severe BPD in extremely preterm infants receiving continuous intravenous infusion of IGF-1/IGFBP-3 (9). Therefore, we could ask ourselves whether or not HIFs stabilizers will offer any additional clinical value.

Interestingly, a recent publication demonstrated that endothelial-targeted inactivation of *Hif-2α* induces emphysema, whereas its overexpression confers protection against emphysema (10). Together, these studies add to many others stressing that cell and molecular maintenance programs necessary for proper alveolar formation are required for maintenance of adult alveolar tissue (2). Therefore, the similarities in pathogenic mechanisms, including sustained inflammation and oxidative stress leading to epithelial and endothelial cell death, and histological features between BPD and emphysema suggest that new therapeutic advances in one of these conditions may be beneficial to the other.

Although the present study provides a better understanding of BPD pathophysiology, important questions remain to be addressed. Indeed, the authors showed that antenatal endotoxin exposure induces RVH, an indirect sign of PH, and that stabilization of HIFs abolished this clinical feature. Because abnormal activation of HIFs is a well-known trigger of vascular remodeling in adult PH, the impact of their stabilization on pulmonary vascular remodeling should be examined. To this end, histological assessment of muscularization/medial thickness of distal pulmonary arteries would be informative. Subsequently, the long-term consequences of HIF stabilization on other organs remains as something to be established.

Relevant to the important science presented in this manuscript, it is also notable that this work product was supported in part by a mentored Alpha Omega Alpha Carolyn L. Kuckein Medical Student Research Fellowship for the first author (Hirsch). Although likely a highly mentored experience and a reflection of the effort of each author in this manuscript, this is a notable achievement worth acknowledging. Developing the next generation of medical scientists is crucial and particularly challenging for potential scientists of all backgrounds. For example, with regard to physicians, a dramatic reduction in the number of physicians pursuing careers in science has occurred over the past 40 years, marked by a staggering ∼70% reduction (11). Programs that support burgeoning physicians, nonphysician scientists, and others interested in medical science are crucial to maintain and revitalize the pipeline of people prepared to lead science into the middle of this century and beyond. This manuscript is evidence of the impact funding programs such as the Kuckein Fellowship can make.

In summary, knowledge gained from the work of Hirsch and colleagues (7) provides new valuable insights into BPD pathogenesis and supports HIFs stabilizers as potential preventive agents. In so doing, the authors highlight the importance of supporting the training of our next generation of scientists. ■

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Prevention of Multidrug-Resistant Tuberculosis in Close Contacts
Back to the Future?

Enormous infectious disease pandemics have bracketed my career in medicine to this point. I entered medical school in the fall of 1981. Just a few months earlier, the first cases of a strange syndrome of previously rare infections began to affect mostly gay men and intravenous drug users in cities in the United States. So began the HIV epidemic. For the first 15–20 years of my career in medicine, AIDS was the dominant infectious disease challenge in the hospitals in which I worked and in many others around the world. Today, for people fortunate enough to have access to medication, treatment provides excellent control of the virus and a satisfactory quality of life for decades. As of this writing, we are in the midst of another infectious disease pandemic, caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus that has so far killed close to 500,000 persons in 2020. Several phase 3 trials of novel and repurposed drugs have been initiated and even completed. At least two vaccine candidates are already in or nearing phase 3 trials, mere months after the first cases of coronavirus disease (COVID-19) were reported.

Throughout this whole period, tuberculosis (TB) has persisted, a stubborn and deadly presence in many countries in the world, mostly in low- and middle-income nations. In 2020, TB will still likely kill more people than any other infectious disease caused by a single pathogen. Effective prevention and treatment of TB has existed for nearly 70 years. That TB remains as a leading cause of morbidity and mortality is a scandal of a particular sort. Even worse, multidrug-resistant strains of TB came to worldwide attention almost 30 years ago (1), but the challenge of multidrug-resistant TB (MDR-TB) is nowhere near under control (2). We are still struggling to discover the best ways to prevent and treat this particular form of the disease—to identify the best combination of antibiotics, dosages, and duration of therapy.

In this issue of the *Journal*, Huang and colleagues (pp. 1159–1168) report a most interesting and curious finding (3). They analyzed data from a prospectively organized cohort of patients in Peru who were exposed in the household to someone with TB and who, if under the age of 19 years, were treated with isoniazid (INH) according to Peruvian national guidelines. Of 4,216 contacts under the age of 19 years, half received INH. This treatment, unsurprisingly, was effective in reducing the overall incidence of active disease that developed in contacts. However, in a very surprising finding, INH also seemed to reduce the incidence of active TB in persons who had been exposed to an index case with MDR-TB, which is by definition resistant to INH. How could this be?

There have been prior reports of the effectiveness of INH in prevention of TB in MDR-TB–exposed persons (4–8), but none of those cohorts were as large or as rigorously analyzed as that in the present study. Two possible explanations immediately come to mind. The first is that the MDR-TB strains to which contacts were exposed exhibited only low-level INH resistance, and even standard preventive doses of INH were able to prevent reactivation in latently infected persons, who harbor a very small organism burden. The authors discount this possibility because they saw no difference in rates of subsequent cases related to INH minimal inhibitory concentrations in the isolates taken from the index case. A second possibility is that before being exposed by the index cases

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