Stolk and colleagues provide the first *in vivo* human evidence that norepinephrine exerts antiinflammatory effects (11). Given that septic shock is associated with profound suppression of a variety of innate and adaptive immune responses, norepinephrine administration may further tip the balance toward impaired immunity in an already vulnerable host. Though norepinephrine remains the best option for the management of vascular dysfunction in septic shock, efforts should be pursued to get the best from its wanted hemodynamic properties while limiting its unwanted immunological side effects. ■

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References

1. Rudd KE, Johnson SC, Agesa KM, Shackelford KA, Tsoi D, Kievlan DR, *et al*. Global, regional, and national sepsis incidence and mortality, 1990-2017: analysis for the Global Burden of Disease Study. *Lancet* 2020;395:200–211.
2. Shankar-Hari M, Phillips GS, Levy ML, Seymour CW, Liu VX, Deutschman CS, *et al*.; Sepsis Definitions Task Force. Developing a new definition and assessing new clinical criteria for septic shock: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). *JAMA* 2016;315:775–787.
3. Levy B, Collin S, Sennoun N, Ducrocq N, Kimmoun A, Asfar P, *et al*. Vascular hyporesponsiveness to vasopressors in septic shock: from bench to bedside. *Intensive Care Med* 2010;36: 2019–2029.
4. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, *et al*. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. *Intensive Care Med* 2017;43: 304–377.
5. Andreis DT, Singer M. Catecholamines for inflammatory shock: a Jekyll-and-Hyde conundrum. *Intensive Care Med* 2016;42: 1387–1397.
6. Stolk RF, van der Poll T, Angus DC, van der Hoeven JG, Pickkers P, Kox M. Potentially inadvertent immunomodulation: norepinephrine use in sepsis. *Am J Respir Crit Care Med* 2016;194:550–558.
7. van der Poll T, Jansen J, Endert E, Sauerwein HP, van Deventer SJ. Noradrenaline inhibits lipopolysaccharide-induced tumor necrosis factor and interleukin 6 production in human whole blood. *Infect Immun* 1994;62:2046–2050.
8. Elenkov IJ, Haskó G, Kovács KJ, Vizi ES. Modulation of lipopolysaccharide-induced tumor necrosis factor-alpha production by selective alpha- and beta-adrenergic drugs in mice. *J Neuroimmunol* 1995;61:123–131.
9. Lyte M, Bailey MT. Neuroendocrine-bacterial interactions in a neurotoxin-induced model of trauma. *J Surg Res* 1997;70:195–201.
10. Lyte M, Freestone PP, Neal CP, Olson BA, Haigh RD, Bayston R, *et al*. Stimulation of Staphylococcus epidermidis growth and biofilm formation by catecholamine inotropes. *Lancet* 2003;361: 130–135.
11. Stolk RF, van der Pasch E, Naumann F, Schouwstra J, Bressers S, van Herwaarden AE, *et al*. Norepinephrine dysregulates the immune response and compromises host defense during sepsis. *Am J Respir Crit Care Med* 2020;202:830–842.
12. Póvoa PR, Carneiro AH, Ribeiro OS, Pereira AC; Portuguese Community-Acquired Sepsis Study Group. Influence of vasopressor agent in septic shock mortality: results from the Portuguese Community-Acquired Sepsis Study (SACiUCI study). *Crit Care Med* 2009;37:410–416.
13. Lamontagne F, Day AG, Meade MO, Cook DJ, Guyatt GH, Hylands M, *et al*. Pooled analysis of higher versus lower blood pressure targets for vasopressor therapy septic and vasodilatory shock. *Intensive Care Med* 2018;44:12–21.
14. Russell JA. Vasopressor therapy in critically ill patients with shock. *Intensive Care Med* 2019;45:1503–1517.
15. Morelli A, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, *et al*. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013;310:1683–1691.

The Elephant Man Meets Pulmonary Hypertension
A Cautionary Tale

Neurofibromatosis (NF) has achieved notoriety because of Joseph Merrick, a medical and sideshow phenomenon in the late 1800s in London who was diagnosed with NF in 1909 (1). His life has been chronicled in several books and films, including the critically acclaimed film *The Elephant Man* in 1980, as well as theatrical productions in both London and New York City. From these, NF became more accepted and investigated (found to be three subtypes: NF1, NF2, and schwannomatosis), and the genetic mutations have been identified (2). Over the years, complications and issues associated with the neurofibromatoses have become apparent. In this issue of the *Journal*, Jutant and colleagues (pp. 843–852) describe a little-appreciated aspect of NF1, pulmonary hypertension (PH) (3).

PH is a rare and incompletely characterized complication of NF1. First described in 1986, the largest previously reported series included just eight patients and was notable for a poor response to PH-specific therapy and poor outcomes (4, 5). Since that report in 2011, individual cases of PH-NF1 have appeared in the literature. In this issue of the *Journal*, Jutant and colleagues, using data from the French Pulmonary Hypertension Network, describe clinical, functional, hemodynamic, and radiographic characteristics as well as responses to pulmonary arterial hypertension (PAH)-specific therapy in 49 cases of PH-NF1, thereby comprising the largest and

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most comprehensive series to date; in fact, this series is greater than the total number of cases of PH-NF1 reported thus far. Though largely confirming many of the smaller previous reports, what emerges from this study not only paints a foreboding picture of PH-NF1 but also raises many additional questions.

PH-NF1 is largely a late complication of NF1 with a median age of diagnosis of 62 years. Interestingly, there is a nearly 4:1 female predominance, in keeping with the female predominance noted in idiopathic and heritable PAH and raising the specter of hormonal influence on disease development (6, 7). Patients largely presented with advanced disease at diagnosis, with New York Heart Association functional class III or IV, 6-minute-walk distances <250 m, and severe precapillary PH by hemodynamics with a mean pulmonary artery pressure of 45 mm Hg, a pulmonary vascular resistance of 10.7 WU, and cardiac index of 2.3 L/min/m^2. Patients with PH-NF1 were poorly responsive to therapy with high mortality (46% 5-yr survival), even in the setting of combination pulmonary vasodilator therapy, including intravenous prostacyclin in some cases.

The poor outcomes and response to therapy that have been previously reported and again confirmed by Jutant and colleagues may be multifactorial and related, in part, to the phenotypic complexity of PH-NF1. Having been associated with vascular remodeling, interstitial lung disease, left heart disease, and skeletal abnormalities leading to secondary restrictive cardiopulmonary physiology, PH-NF1 is quite deservedly classified as World Health Organization group 5 PH, PH secondary to unclear/multifactorial mechanisms (5, 8, 9). Indeed, in the cohort presented by Jutant and colleagues, pulmonary parenchymal involvement was noted in 40 of the 41 patients with interpretable high-resolution computed tomography scans. This observation, in combination with the frequent hypoxemia noted at diagnosis in the cohort, suggests a prominent role in the pathophysiology from parenchymal lung involvement; yet, 27 patients had normal spirometry and lung volumes. Interestingly, the predominant pulmonary function test abnormality was a severely reduced diffusion capacity of the lung for carbon monoxide, likely speaking to the significance of pulmonary vascular involvement in the overall phenotype but certainly not excluding some form of parenchymal involvement.

More interesting still, of the three available pathologic samples in the cohort, parenchymal abnormalities as well as severe arterial and venous remodeling were noted in all samples, the latter most concerning for a pulmonary venoocclusive disease like pathophysiology with subsequent implications for poor response to PAH-specific therapy (10, 11). Though it is unlikely that three samples are fully representative of the pathologic spectrum of PH-NF1, these findings corroborate what has been previously reported in other series and, taken together, speak to the phenotypic heterogeneity present in PH-NF1 (4, 9).

Because of the functional and hemodynamic severity of the PH in this cohort, the physicians caring for them ultimately opted to treat 45 of the 49 patients with PAH-specific medications, including 44% treated with combination pulmonary vasodilator therapy on second follow-up and 64% on the last reassessment. With this modern-era PAH treatment regimen, despite improvements in hemodynamics and New York Heart Association functional class, hypoxemia worsened irrespective of the severity of spirometry or lung volume abnormalities by pulmonary function testing, and 6-minute-walk distance remained unchanged initially but decreased below baseline at the last reassessment. Even more concerning, however, is that during the course of treatment with PAH-specific therapy, three patients died suddenly at home of unclear causes, and overall mortality was much higher in the PH-NF1 cohort compared with the their idiopathic PAH counterparts (12). Thus, despite some evidence of short-term benefit, routine treatment of these patients with currently available PAH-specific medications cannot be recommended. Rather, based on available observations, it seems more prudent to focus on nonspecific treatment with oxygen and diuretics as indicated with early referral for lung transplant in those who are eligible.

Although we congratulate the authors for the most complete description to date of PH-NF1 and the largest cohort presently available, it is still a relatively small, retrospective sample. Despite this, it seems that PH remains a rare, phenotypically heterogeneous complication of NF1 with poor outcomes and no conclusive data to support treatment with pulmonary vasodilators. Increased awareness of PH-NF1 among providers with a low threshold for screening echocardiogram, high-resolution computed tomography, and right heart catheterization when indicated among symptomatic patients is imperative to target earlier diagnosis and may help amass larger cohorts that can be studied prospectively to devise treatment regimens to improve short- and long-term outcomes.

As for Mr. Merrick, we bet you thought we were going to tell you that he died from what appeared to be PH; alas, no—he died from asphyxiation. Moreover, although his physical condition was long attributed to NF1, some researchers believe that he may actually have suffered from the even rarer Proteus syndrome; however, despite genetic analysis of his hair and bone in 2003, the exact etiology of his deformities has never been conclusively established (13). ■

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References

1. Howell M, Ford P. The true history of the elephant man. 3rd ed. London: Penguin Books; 1992.
2. Rasmussen SA, Friedman JM. NF1 gene and neurofibromatosis 1. *Am J Epidemiol* 2000;151:33–40.
3. Jutant E-M, Jaïs X, Girerd B, Savale L, Ghigna M-R, Perros F, *et al*. Phenotype and outcomes of pulmonary hypertension associated with neurofibromatosis type 1. *Am J Respir Crit Care Med* 2020;202: 843–852.
4. Porterfield JK, Pyeritz RE, Traill TA. Pulmonary hypertension and interstitial fibrosis in von Recklinghausen neurofibromatosis. *Am J Med Genet* 1986;25:531–535.
5. Montani D, Coulet F, Girerd B, Eyries M, Bergot E, Mal H, *et al*. Pulmonary hypertension in patients with neurofibromatosis type I. *Medicine (Baltimore)* 2011;90:201–211.
6. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, *et al*. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med* 2006;173:1023–1030.

7. Austin ED, Cogan JD, West JD, Hedges LK, Hamid R, Dawson EP, *et al*. Alterations in oestrogen metabolism: implications for higher penetrance of familial pulmonary arterial hypertension in females. *Eur Respir J* 2009;34:1093–1099.
8. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, *et al*. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J* 2019;53:1801913.
9. Jutant E-M, Girerd B, Jaïs X, Savale L, O'Connell C, Perros F, *et al*. Pulmonary hypertension associated with neurofibromatosis type 1. *Eur Respir Rev* 2018;27:180053.
10. Montani D, Price LC, Dorfmuller P, Achouh L, Jaïs X, Yaïci A, *et al*. Pulmonary veno-occlusive disease. *Eur Respir J* 2009;33:189–200.
11. Humbert M, Maître S, Capron F, Rain B, Musset D, Simonneau G. Pulmonary edema complicating continuous intravenous prostacyclin in pulmonary capillary hemangiomatosis. *Am J Respir Crit Care Med* 1998;157:1681–1685.
12. Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Muros-Le Rouzic E, *et al*. Five-year outcomes of patients enrolled in the REVEAL registry. *Chest* 2015;148:1043–1054.
13. Tibbles JA, Cohen MM Jr. The proteus syndrome: the elephant man diagnosed. *Br Med J (Clin Res Ed)* 1986;293:683–685.

On Genetics, Lung Developmental Biology, and Adult Lung Function

A hypothesis is nothing but a hypothesis until proven. The fetal origins of disease hypothesis, formally the Developmental Origins of Health and Disease hypothesis, postulates that early life events may have a long-term impact on diseases and traits in adulthood (1). Such events, including environmental exposures, and developmental or pathophysiologic processes, may take place *in utero*, perinatally, or during childhood. Evidence is now accumulating that supports the Developmental Origins of Health and Disease hypothesis in that factors underpinning lung disease risk in adulthood act in early life (2–4).

In this context, Portas and colleagues (pp. 853–865) report in this issue of the *Journal* associations between lung developmental genes and adult lung function using the U.K. Biobank (5). They make use of lung development biology knowledge, selecting candidate genes to explore associations with lung function indices (Figure 1), rather than starting with an agnostic genome-wide association study (GWAS) analysis, currently a standard approach.

In the study by Portas and colleagues, almost 350,000 subjects with mean age 56 years (range, 39–70 yr) contributed cross-sectional lung function data from the well-powered U.K. Biobank (6, 7). The list of genes related to lung development was prepared by two authors, summarizing both human and experimental data in a variety of model organisms. In addition, this list was further extended to include relevant genes based on pathway information from four databases. In total, 391 genes (represented by 106,384 variants) believed to influence lung development were tested for association with prebronchodilator FVC and FEV_1/FVC. Using a two-stage and "best SNP per gene" approach, novel independent signals from 36 genes were identified and replicated internally; 16 were uniquely associated with FVC, 19 were uniquely with FEV_1/FVC, and only one signal was associated with both traits. Next, the authors used meta-analysis data from previous GWASs in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) and SpiroMeta consortia ($n > 100{,}000$ in both datasets) and replicated 16 variants. Pathway analyses revealed that identified genes belong primarily to the following pathways: growth factors, transcriptional regulators, cell–cell adhesion/cytoskeletal, and extracellular matrix, which was not surprising given the fact that genes were preselected based on involvement in lung development in the first place. Finally, a majority of the key SNPs were found to influence expression in the blood and/or lung tissue.

The results emerging from this methodologically sound sequence of analyses have important implications. If the missing heritability of complex traits resides at least partly in genetic variants that are missed by traditional genome-wide significance thresholds, using *a priori* knowledge to reduce the search space may be an effective approach to retrieve these missing genomic components. Using this hypothesis-driven approach, which is reminiscent of the classical candidate gene or pathway study, this study identified 16 novel variants associated with lung function that were sufficiently robust to survive both internal and external replication. Of note, although all these variants were significant after Bonferroni correction, only a few of them reached genome-wide significance in the U.K. Biobank, and none did in the external replication. Therefore, this approach identified successfully multiple novel robust genetic variants for lung function that could have been missed in a traditional GWAS. Naturally, any approach that is based on *a priori* knowledge is as good as the knowledge on which it is based. Although the authors did try to formalize their selection process of genes, it should be noted that this process eventually boils down to expert opinion and the integration of data from animal and human studies, which could be perceived as subjective. Future approaches guided by single cell–specific transcriptomic signatures obtained during different stages of lung development may represent another way to select genes and limit the search space of a GWAS (8).

Complex traits are complex not only because of their multifactorial nature but also because of their phenotypic heterogeneity. Lung function impairment is no exception, as it is associated with different profiles of risk factors and morbidities (and genetic determinants) depending on whether the "impairment" refers to FEV_1, FVC, or their ratio. Not surprisingly, in the study by Portas and colleagues, the vast majority (97%) of the identified susceptibility genes affected either FVC or FEV_1/FVC uniquely, and only one variant was associated with both indices. Although deficits in FEV_1/FVC identify the obstructive pattern and are the hallmark of chronic obstructive pulmonary disease (COPD), low levels of FVC in the presence of a conserved ratio could

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