situations, both from residents and military personnel, to characterize direct and epigenetic consequences of exposure that may impact large populations in both the short and long term (11). Planning ahead to understand how exposures cause disease will be critical, and, ideally, such knowledge would prevent further use of chemicals or agents identified and designated as respiratory toxins.

If mistakes of the past are not heralded as lessons, then they are destined to be repeated. When it comes to global respiratory threats as but one consequence of armed conflict, we have much to learn and many lessons to learn from. As clinicians working to prevent and treat lung disease, it is clear that advocating to prevent long-term respiratory perils of war falls quite clearly in our lane. ■

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Of Registries and Disease Classification: Unmasking the Challenges of Pediatric Pulmonary Hypertension

Despite major advances in diagnostic strategies and drug therapies over the past decades, pulmonary hypertension (PH) continues to cause significant morbidity and mortality in diverse pulmonary, cardiac, hematologic, and other systemic disorders in neonates, infants, and children (1, 2). Evidence-based advances in the care of children with PH have been limited due to many challenges, including the heterogeneity of associated conditions; lack of organized multidisciplinary care centers in the past; small numbers of patients at each center; a paucity of quality endpoints for assessing clinical course and response to therapy; and many other factors (1–3). Importantly, despite strong clinical evidence from multicenter randomized trials supporting the use of several PH-targeted drugs for adults, data supporting the safety and efficacy of these agents remains extremely limited for pediatric PH. Clearly, many similarities between adult and pediatric PH exist; however, critical aspects of PH in children can be

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quite distinct, as pediatric PH is intrinsically linked to issues and disorders related to lung growth and development, including perinatal genetic and epigenetic influences, as well as marked differences in disease epidemiology, pharmacokinetics and drug metabolism, and other features. Unfortunately, studies that address the safety and efficacy of PH therapies in children are rare, as most pharmaceutical studies have focused on the adult population and only in patients with a limited range of associated conditions (4).

Overall, pediatric PH has been understudied, research has been poorly funded, and major gaps in our knowledge of the natural history, mechanisms of disease and treatment of disease-specific forms of childhood PH persist. Both short-term and long-term strategies are needed to enhance the diagnosis, management, and prevention of PH in children. These include the need for: *1*) identification of current gaps in our basic knowledge of normal and impaired lung vascular development and interactions between vascular and alveolar growth; *2*) better characterization of unique aspects of the developing pulmonary circulation and related basic mechanisms underlying pediatric PH, including differences in epidemiology and drug pharmacokinetics and dynamics; and *3*) overcoming barriers that limit the successful translation of basic science findings to clinical trials and improving outcomes of children with PH or related PVD. Over the past decade, increasing awareness of the lack of knowledge regarding the diversity of diseases associated with PH, disease frequency, natural history, short and long-term outcomes, current diagnostic and therapeutic strategies in disease and age-specific settings, and others has led to the development of patient registries for research and developing clinical care consortiums, in addition to the development of guidelines and growing efforts to accelerate the development of novel therapeutic strategies for PH care, including translation of PH drugs to children in diverse settings as well as targeting novel endpoints and developing new therapies. As a result, there is clearly a need for more information provided through large registries and related datasets, especially as organized according to established classification systems.

This recent publication in this issue of the *Journal* (pp. 758–766) from the team at the Great Ormand Street Hospital for Children (GOSH) provides a unique window into the nature of pediatric PH by characterizing the longitudinal outcomes of incident cases from throughout the UK over a very extensive time period (5). In addition to advancing many important findings from a very comprehensive dataset, this study further offers a timely and wonderful opportunity to recognize the 20th anniversary of this internationally renowned service, as originally established and led by Dr. Glennis Haworth, whose contributions to pediatric PH have been extraordinary. A leader who emphasized the highest standards of academic work in the field, Dr. Haworth was one of the earliest and strongest advocates for improving outcomes of children with severe disease (6). Now strongly led by Dr. Shahin Moledina, the GOSH experience reflected in this report provides important new data on pediatric PH as based on the comprehensive nature of the care network provided by the UK national service in partnership with referral physicians. The comprehensive nature of the UK national referral service, the enrollment of consecutive prevalent cases over a very extensive length of time coupled with frequent clinical follow-up and close communications with referring physicians provides a unique and complete cohort in the UK registry that has not been previously matched. Additional strengths of this study include the very high quality of data that includes extensive assessments of incident patients throughout their clinical course, which provides strong data on critical outcomes related to survival, lung transplantation, and in some disorders, time to PH resolution in children.

Whereas data from past registries have provided important insights into pediatric PH, there have been many limitations due to selection bias, inclusion of prevalent with incident cases, and incomplete data due to the many challenges of fragmented care in some health systems. This paper further reminds us of the importance of registries as applied to current standards for disease characterization according to the World Symposium in Pulmonary Hypertension (WSPH) Classification System (2, 7). Registries of patients with PH have been instrumental in characterizing the presentation and natural history of the disease and provide a basis for prognostication. (8–12) Rigorously managed registries provide essential data that serves as an effective tool to define disease course, co-morbidities, and late outcomes. Many findings support observations from a recently published characterization of pediatric PH from the Pediatric Pulmonary Hypertension Network (PPHNet) Registry (12). For example, the PPHNet registry clearly demonstrated that greater focus is needed in the children with lung associated PH (WSPH Group 3), which constitutes well over half of the cases of pediatric PH, including key developmental lung disorders such as bronchopulmonary dysplasia, congenital diaphragmatic hernia, Down syndrome, alveolar capillary dysplasia, and a growing list of others (12). These disorders represent just the "tip of the iceberg" for this problem, and the vital importance to address diverse aspects of PH in children, especially in preterm newborns and young infants.

In recognition of the need for more effective classification systems for children, the Pediatric Task Force of the Pulmonary Vascular Research Institute (PVRI) designed a classification system that may recognize distinct patterns of disease and clinical features that warrant being considered for a pediatric-specific system (13). However, early experience suggests persistent issues with its applicability due to gaps regarding its complexity, inconsistent subgrouping and overlaps between major disease categories, which suggest the need for developing a novel, pediatric system to achieve its goals. In addition, it has become increasingly clearer that traditional means of identifying and characterizing disease are insufficient to define subgroups of patents whose natural history more precisely, response to therapy and ultimate outcomes may be optimized through the application of novel 'omics strategies for more comprehensive characterization of patients to improve outcomes through enhanced precision care as well as with improved clinical trial design (14, 15). This further highlights the need to develop classification systems that serves multiple missions to determine what is best for the clinical team performing the initial diagnostic evaluation, investigators to more precisely study natural history, pathobiology and optimal therapies, and teams with industry and regulatory agencies to enhance clinical trial design through more precise phenotypes. The latter will require progressive ability to link clinical features with advanced endotyping that includes various genetics, genomic, and proteomic strategies in the future. ■

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Continuous Positive Airway Pressure and Cardiovascular Risk Reduction in Patients without Excessive Sleepiness

Importance of the Pulse Rate Response

Subgroup analyses of cardiovascular prevention trials in obstructive sleep apnea (OSA) may play an important role in patient selection for future trials. In the intention-to-treat analysis of the RICCADSA (Randomized Intervention with Continuous Positive Airway Pressure in coronary artery disease (CAD) and OSA) randomized controlled trial (RCT), CPAP failed to reduce adverse cardiovascular outcomes in nonsleepy patients with OSA and CAD (1). In this issue of the *Journal*, Azarbarzin and colleagues (pp. 767–774) report a secondary analysis of the RICCADSA RCT to test for heterogeneity of CPAP effect on the basis of pulse rate response to respiratory events (ΔHR) (2). Using a multivariable Cox regression as their

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