evaluating for psychiatric disorders are the two most useful steps. Because depression, anxiety, and somatization are the most common psychiatric disorders associated with dizziness, these can often be evaluated and even treated by a primary care physician, referring only the more severe or refractory cases to a mental health specialist. Various types of vestibular testing, including electronystagmography, rotatory chair, dynamic posturography, and clinical evaluation, can be done by a neuro-ophthalmologist or neuro-otologist. Whether any one of these tests is superior to the others or how often such testing actually changes patient management is unclear.

Dizziness is rife with questions for primary care researchers. Does dizziness associated with treatable psychiatric disorders such as depression and anxiety respond to psychotropic medication or psychotherapy? Can dizziness attributable to a chronic vestibulopathy improve with vestibular rehabilitation, or is it an irreversible symptom that must be tolerated, in the words of Jonathan Swift, "That old vertigo in his head/Will never leave him till he's dead"? One positive study of vestibular rehabilitation showed relatively modest and inconclusive benefits.[10] Is one type of vestibular testing superior to another, and does such testing make a difference in clinical management and patient outcome? What is the role of subspecialists, such as neurologists and otolaryngologists, in the care of dizzy patients, and which patients benefit from referral? Can we reduce the amount of laboratory testing, neuroimaging, and other low-yield tests without adversely affecting patient outcome? Are meclizine, other antihistamines, and anticholinergic medications beneficial in any type of dizziness other than acute and prolonged vertiginous attacks? While the disorder often resolves, its persistence in a considerable minority of patients causes substantial suffering and functional impairment.[11] As a physical symptom for which patients' self-reporting is the gold standard, dizziness will always be difficult to study, and our research findings will have rougher edges than in many other areas of clinical investigation. But as long as dizziness crosses the clinic threshold as often as it does—10 million visits annually in the United States alone—imperfect answers that are even a slight improvement over previous imperfections are worth the investment.

KURT KROENKE, MD
Department of Medicine
Uniformed Services University of the Health Sciences
Bethesda, Maryland

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Surfactant Replacement Therapy—Room for Improvement

WE BREATHE EFFORTLESSLY because of pulmonary surfactant. Unfortunately, very premature infants lack surfactant and have labored breathing and respiratory insufficiency. Medical conditions associated with alveolar instability and microatelectasis are prime candidates for surfactant replacement therapy. Surfactant replacement therapy for preventing and treating the respiratory distress syndrome in newborns is a major therapeutic advance in neonatal care and is comprehensively reviewed by Poulain and Clements elsewhere in this issue.[1] Pulmonary surface-active material is composed of phospholipid, cholesterol, and associated surfactant proteins, which are designated SP-A, SP-B, and SP-C.[2] There is a fourth surfactant-associated protein, SP-D, that binds to surfactant weakly and is physiologically a host-defense molecule.[3] Surfactant is synthesized by alveolar type II cells and packaged in lamellar inclusion bodies. After secretion by endocytosis, this material unravels to form tubular myelin, a unique physical form of surfactant, and then adsorbs to the air-liquid interface. Surfactant proteins A and B are necessary for the formation of tubular myelin. They organize the three-dimensional structure of the phospholipids. Adsorption occurs during inhalation when the surface film is expanded, and during exhalation a low surface tension is formed when the surface film is compressed. After repeated respiratory cycles, some of the lipids of surfactant are squeezed from the air-liquid interface, enter the subphase, and are endocytosed by type II cells for reuse. The uptake of extracellular surfactant by type II cells is facilitated by SP-A.

The development of surfactant for replacement therapy underscores the importance of basic science in providing a framework for clinical science. The initial physiologic studies that showed that a low surface tension was present at the air-liquid interface in the lung was reported by von Neergard in 1929. This observation was not widely appreciated, however, and had to be rediscovered in the 1950s. At that time Pattle and Clements independently isolated and identified surfactant as the substance that produced the low surface tension in the lung and defined its physical properties.[4,5] This basic science precept was then rapidly applied to a clinical situation. Within three years surfactant was reported to be deficient in the lungs of infants who died of hyaline membrane disease.[6]

Soon the unusual phospholipid that was responsible

for the low surface tension, dipalmitoyl phosphatidylcholine (DPPC), was identified in surfactant. The logical next step was to administer DPPC to infants with the respiratory distress syndrome, and this was accomplished in the early 1960s. The clinical trial with liposomes of DPPC failed, however.[7] In retrospect, the trial failed because the critical importance of the adsorption of DPPC to the air-liquid interface was not appreciated at the time. Later it was found that the proteins of surfactant or other amphipathic molecules such as long-chain alcohols were necessary for the rapid adsorption of surfactant to the surface film. Dipalmitoyl phosphatidylcholine by itself adsorbs to an air-liquid interface over hours, but adding unsaturated phospholipids and the surfactant proteins can speed the adsorption rate to seconds. If our breathing rate is 12 times per minute, adsorption must occur within a few seconds to provide the low surface tension at the end of the next exhalation.

There is no doubt that the preparations of surfactant for replacement can be improved. Current studies on the structure-functions relationship of the surfactant proteins will lead to a better understanding of how they regulate phospholipid organization and movement at the air-liquid interface and ultimately to the next generation of surfactant formulations for replacement therapy. Basic science has led to a better understanding of the role of surfactant proteins on phospholipid trafficking in the alveolus and provided reagents for diagnosing new diseases. For example, a subset of infants with respiratory distress has been shown to be deficient in surfactant protein B.[8,9] Likely genetic variants in the other surfactant proteins will be discovered in the next few years. Tools will become available for gene therapy and new modes of therapy using the surfactant proteins or genes to express them over the next decade.

The surfactants that are currently used for replacement therapy can be divided into two groups. The group designated natural surfactants comprises extracts of minced lung or pulmonary lavage and includes the two hydrophobic surfactant proteins, SP-B and SP-C. The other group, the artificial surfactants, does not contain these proteins. Soon there will be additional surfactant preparations that will contain synthetic peptides or modified recombinant proteins that mimic the natural proteins. In animals born prematurely or with acute lung injury, natural surfactants appear to have physiologic advantage over the current synthetic surfactants.[10] Superior clinical efficacy in direct comparison has not been demonstrated to date.

Surfactant replacement therapy for the prevention and treatment of the respiratory distress syndrome in newborns has changed the care of premature infants and has shown the need for early, prompt therapy.[11] Although prophylactic treatment of very small infants is most effective, treatment after the respiratory distress begins (rescue therapy) is nearly as effective. In either case, there is a reduction in mortality and in the incidence of pneumothoraces or air leak presumably due to reduced airway pressures during mechanical ventilation. There is no decrease in the incidence of intraventricular hemorrhage or the number of babies in whom bronchopulmonary dysplasia develops. There also is no increase in the number of babies with bronchopulmonary dysplasia, as might be envisioned if the treatment were only slightly effective. Initially there was concern that the treatment, if successful, would produce a large cohort of severely handicapped babies. This has not occurred, but the survivors do show substantial physical impairment and learning disabilities, and there is room for an improved outcome.[12]

Surfactant replacement therapy for other diseases is just beginning. Surfactant dysfunction plays an important role in the pulmonary manifestation of the adult respiratory distress syndrome (ARDS). This fact was clearly recognized at the time the syndrome was designated.[13] Surfactant recovered from patients with ARDS is abnormal in its ability to lower surface tension and composition.[14,15] Studies of surfactant replacement therapy in patients with ARDS are still in the pilot stage; surfactant replacement will likely improve pulmonary compliance and gas exchange.[16,17] Further studies will be needed to show the role of surfactant replacement therapy on mortality, the prevention of the extrapulmonary manifestations of ARDS, and the development of chronic lung disease.

Surfactant is not restricted to the alveolar spaces, but is also found in small airways. Enhorning and Holm have developed a theoretical and physiologic rationale for the important role of surfactant in small airways.[18] Surfactant is needed to prevent small airway collapse and for high pressure to open liquid-filled airways. In addition, by immunocytochemistry and in situ hybridization, the nonciliated bronchiolar cells of rodents express the surfactant proteins A, B, and D. The precise function of these proteins in small airways is not known, but a likely function for SP-A and SP-B is in the movement and organization of surfactant in small airways. Although definitive clinical studies have not been reported, it is certainly possible that exogenous surfactant will find a place in the treatment of acute severe asthma.

Improvement in the treatment of ARDS and bronchopulmonary dysplasia will likely require the addition of other pharmacologic agents. Surfactant can stabilize the alveoli and may prevent the loss of gas-exchange units by lessening the apposition and fusing of atelectatic denuded alveolar walls. This will do little to repair damaged epithelium or clear the alveolar exudate, however. One of the critical features of acute lung injury is the loss of many alveolar type I cells, the flat squamous cells that cover most of the alveolar wall. In wound healing, the epithelium must be restored to prevent the outgrowth of fibroblasts. This would be facilitated by exogenous growth factors, especially growth factors that stimulate epithelial proliferation but not mesenchymal cell proliferation such as keratinocyte growth factor.[19] After the alveolar epithelium is reestablished, treatment could focus on stimulating the transport of fluid from the

alveolar space into the interstitium. Transepithelial transport can be stimulated by β-adrenergic agents and can increase the rate of clearance of pulmonary edema when the alveolar epithelium is intact.[20]

Exogenous surfactant has additional possible pharmacologic uses. It could be useful for delivering lipophilic drugs such as cyclosporine for patients with lung transplants. Finally, because SP-A binds to alveolar type II cells and stimulates endocytosis, it may be useful to target vectors for gene therapy for the alveolar epithelium. A vector with SP-A protein as an external ligand could theoretically be used to target the SP-B gene to type II cells in infants whose respiratory distress syndrome is caused by a lack of SP-B.[9]

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ROBERT J. MASON, MD
Department of Medicine
National Jewish Center for Immunology and Respiratory Medicine

Division of Pulmonary and Critical Care Medicine
University of Colorado School of Medicine

Denver, Colorado

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