Early Neonatal Research at Wilford Hall US Air Force Medical Center

The beginning of the many contributions to the field of neonatology originating from Wilford Hall Air Force Medical Center began when Robert deLemos, MD (Col, retired US Air Force [USAF]), was assigned to Lackland Air Force Base (AFB) in the summer of 1969. When Dr deLemos came to Texas, he was the first and only fully trained Air Force neonatologist at a time when neonatal medicine was still just in its infancy. Although surfactant deficiency had been described as the cause of hyaline membrane disease by Dr Avery in her landmark article published in 1959, surfactant replacement therapy in premature infants did not begin until the 1980s after the work of Dr Fujiwara et al was reported in *Lancet*.1,2 Morbidity and mortality remained high in premature infants, especially in those under 1500 g with respiratory distress syndrome (RDS). Reports published in the 1960s and 1970s described early attempts at the use of mechanical ventilation to rescue neonates with respiratory failure, but ventilator options were limited and devices were not widely available, resulting in minimal success.3,4 Given this backdrop, the story of the accomplishments of a relatively small group of military neonatologists led by Dr deLemos takes on added historical significance.

Some of the most important initial work completed by Dr deLemos and his colleagues centered on their efforts to improve respiratory support and cardiovascular monitoring in the critically ill neonate. In the late 1960s and early 1970s, physiologic monitoring of the neonate was very difficult. Blood pressure could only be accurately obtained by using indwelling arterial lines. Ventilators in this time period only provided flow during the inspiratory cycle. If patients breathed between ventilator breaths, they were rebreathing their own exhaled gas contributing to impaired ventilation and oxygenation. In neonates this required mechanical ventilation at rapid rates imposing a greater risk of lung trauma and cardiac and central nervous system complications. Additionally, positive end-expiratory pressure (PEEP) was not a feature of available neonatal ventilator systems. The end result was that assisted ventilation of the preterm infant with surfactant deficiency was of little to no benefit in improving outcome.

In an effort to come up with a better solution, Dr deLemos, along with Bob Kirby, MD (Col, retired USAF), an anesthesiologist, and Jimmy Schultz, RRT, embarked on a course of developing an effective pediatric/neonatal ventilator. The initial device was built by Jimmy Schultz by using spare parts from predominantly a Mark II ventilator. The original request from Drs Kirby and deLemos of Jimmy Schultz was to build a ventilator that allowed for a continuous flow of fresh gas through all phases of the respiratory cycle, thus allowing for a consistent level of oxygen and humidification as well as rapid removal of exhaled CO₂. Additionally, they wanted a device capable of providing continuous PEEP during the

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ABBREVIATIONS

AFB—Air Force Base
ECMO—extracorporeal membrane oxygenation
HFOV—high-frequency oscillatory ventilation
HFV—high frequency ventilation
IMV—intermittent mandatory ventilation
PEEP—positive end-expiratory pressure
RDS—respiratory distress syndrome
USAF—US Air Force

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expiratory phase. They also requested that the ventilator be able to provide a peak pressure up to 80 cm H2O, PEEP up to 20 cm H2O, and rate up to 130 breaths per minute to support small children weighing up to 25 kg in addition to premature infants weighing as little as 800 g. Because patients supported with this device were able to breathe fresh (not expired) gas with spontaneous respirations between machine breaths, this meant that fewer mechanical breaths could be used. With the development of this prototype neonatal ventilator, intermittent mandatory ventilation (IMV) for the neonate was born.

Using their prototype ventilator, Kirby et al went on to demonstrate that neonates with respiratory failure could be kept in a physiologic pH range without the need of paralytic agents or complex triggering devices. This allowed for ease of weaning the ventilator rate and better determination of when a patient could be extubated. In 1970 Kirby et al mechanically ventilated 90 infants with their new device, including 60 infants given a diagnosis of RDS for periods ranging from <24 hours to 31 days. No infant was ventilated unless the combined pediatric and anesthesia staffs felt they would not survive without support. Criteria for intubation were a PaO2 of <40 mm Hg on 100% oxygen, a Paco2 of 70 mm Hg and rising, and/or repeated apneic episodes of a life threatening nature. These extreme criteria for intubation were used as assisted ventilation was thought to contribute little to the survival of the preterm infant. At a time when survival was typically <30% for infants with severe RDS, Wilford Hall was surviving 60% of mechanically ventilated infants with RDS with birth weights as low as 750 g and up to 80% of infants 1600 g or greater. After the early success of the prototype ventilator, individuals from Bourns (a leading manufacturer of mechanical ventilators during this era) were contacted to see if they were interested in helping to further develop the Wilford Hall device; however, as Dr deLemos later related, they were uninterested given their belief that there was only a limited need for neonatal ventilators in the United States (~100), and Bourns had close to this number of LS 104 devices already built. Shortly thereafter, Dr Forrest Bird paid a visit to Wilford Hall. Impressed with the success that Drs deLemos and Kirby had in ventilating ill premature infants, he became interested in their device. This encounter subsequently led to Dr Bird further refining the Wilford Hall prototype ventilator and eventually marketing it as the Baby Bird ventilator.

From the early 1970s into the 1980s, the Baby Bird proved to be the workhorse mechanical ventilator used for the management of neonates and infants with RDS and other causes of respiratory failure. During this time, IMV remained the predominant form of ventilatory support until the development of synchronous IMV over the last 15 to 20 years. Nonetheless, to this day, the use of both continuous gas flow during expiration and the inclusion of PEEP remain standard in the design of neonatal ventilatory support. The ventilator initially developed by the military team of deLemos, Kirby, and Schultz proved to be an exceptional device that revolutionized mechanical ventilation of the neonate and small child. A photograph of Dr deLemos is pictured in Fig 1, the prototype ventilator built by Jimmy Schulz in Fig 2, and the original Baby Bird device built by Dr Bird in Fig 3.

During the early days of experimentation with assisted ventilation of the neonate at Wilford Hall, additional novel work was reported by Dr deLemos and colleagues. Among their many contributions, one of the most important was their landmark article published in 1973 describing the beneficial effects of continuous positive airway pressure combined with mechanical ventilation, what we now call PEEP. In this report of 25 mechanically ventilated neonates, deLemos et al analyzed the effects of PEEP by increasing support from 0 to 20 cm H2O in 5-cm increments. They
were able to demonstrate improved oxygenation in 80% of patients with increasing PEEP. Of particular importance, they also described in this study the adverse effects of high levels of PEEP (decreased blood pressure and increased PaCO2 generally occurring above 10 cm H2O), noting the principle that just because some is good, more is not always better. The authors recommended that the level of PEEP selected must therefore be individualized for each patient by careful monitoring of blood pressure, chest radiographs, and blood gas measurements.

In the 1970s noninvasive blood pressure measurement with a stethoscope and sphygmomanometer was ineffective in the neonate because newborn arteries do not generate an adequate sound for auscultation. Systolic blood pressure was typically estimated by determining when the arm “pinned up” as pressure was released via the sphygmomanometer. This was a very poor technique for the preterm or ill term infant whose extremities often looked dusky to begin with. Among larger patients indwelling catheters were used to monitor blood pressure; however, umbilical arterial lines could not be placed in many seriously ill newborns, and angiocaths small enough for an infant’s peripheral artery did not exist.

In an effort to improve existing technology to measure blood pressure, Dr Gary McLaughlan, a fellow at the time under Dr deLemos, devised a novel device that used Doppler ultrasound to indirectly measure blood pressure in neonates. In 1971, Dr McLaughlan published the Wilford Hall experience with this device in 15 ill newborns demonstrating its accuracy in comparison with blood pressures measured from indwelling umbilical catheters. Similar to the Baby Bird ventilator, this early prototype developed at Wilford Hall subsequently led to the marketing of a commercially available device that greatly advanced the standard of care available at the time for monitoring critically ill infants. Figure 4 shows the Doppler pressure device used in Dr McLaughlan’s original study.

Transport has always played a vital role in the military pediatric mission, with many technological advances in this arena originating early on in San Antonio through the collaborative efforts of military personnel at Wilford Hall, Brooke Army Medical Center and Brooks AFB. Interest in reliable and safe pediatric transport grew out of the need to support local, regional, and intercontinental movement of critically ill infants from outlying military bases to Wilford Hall and Brooke Army Medical Center often for definitive life-saving care. Specifically, in the area of neonatal transport, military physicians were instrumental in developing, testing, and modifying neonatal equipment ensuring that it performed safely while not interfering with aircraft electromechanical operations.

Howard Heiman, MD (COL, retired US Army), in conjunction with Airborne Life Support and the testing laboratory at Brooks AFB, developed the first fully contained neonatal transport unit that continues to be the model for systems routinely used today. These systems have been effectively used in the military neonatal care system for several decades, supporting both regional and long distance transports from as far away as Asia and Europe.

Over the years, there has remained a strong interest at Wilford Hall in advancing the management of neonates with respiratory failure in an effort to reduce acute and chronic lung injury. In the early 1980s Drs Null, deLemos, Yoder (Col, retired USAF), and Clark began working with high frequency ventilation (HFV) aiming to improve survival and reduce bronchopulmonary dysplasia in newborns. These investigators were instrumental in establishing a term and preterm baboon model along with their colleagues at the Southwest Foundation for Biomedical Research in San Antonio that proved to be invaluable for studying HFV. By using the baboon model coupled with clinical experience...
generated from the Wilford Hall NICU. Dr Null and his colleagues were able to develop an appropriate HFV strategy for the management of RDS and other causes of respiratory failure in the newborn. Numerous publications were generated from the Wilford Hall experience with HFV, where the clinical use of HFV dates back to late 1983.\textsuperscript{10–26} Of note, HFV research was conducted by using both the Bird volumetric diffusive ventilation flow interrupter and Texas Research high frequency oscillator, the latter of which served as the prototype for the Sensormedics 3100A.

One of the first HFV randomized controlled clinical trials conducted at Wilford Hall was led by Dr Reese Clark in the mid 1980s involving very low and extremely low birth weight premature infants.\textsuperscript{27} The findings from this trial were extremely important at the time in that they demonstrated that HFV could be safely used in premature infants to significantly decrease bronchopulmonary dysplasia without adverse complications, findings quite disparate from earlier reported studies involving other centers. The many studies and publications from the San Antonio military neonatal community such as the Clark study were integral to the further development of HFV and ultimate Food and Drug Administration approval in the early 1990s, particularly high-frequency oscillatory ventilation (HFOV). Today, HFOV devices are nearly universally present in newborn and pediatric intensive care units not only in the United States but throughout the world. It is important to recognize that an understanding of the utility of HFV was only made possible by the dedication of many Wilford Hall neonatology staff and fellows who spent countless hours at the bedside of critically ill patients, using trial and error to gain insight into different HFV devices and their effect on treating varying underlying lung pathophysiology.\textsuperscript{28} A present day Sensormedics HFOV 3100A is pictured in Fig 5.

In continuation of the tradition of excellence established early on at Wilford Hall in managing critically ill newborns, especially those with cardiopulmonary problems, Devin Cornish, MD, also a fellow under Dr deLemos, in late 1984 initiated steps to start an extracorporeal membrane oxygenation (ECMO) program. At this time, ECMO was considered largely an experimental therapy and was only being offered at a few centers within the United States. A story that very few people know even today, however, is that in 1972 a neonate dying of respiratory failure was successfully placed on extracorporeal bypass with a membrane oxygenator in the NICU at Wilford Hall by Dr deLemos (see Fig 6). Even though this patient eventually died, this case is remarkable in that Dr deLemos was even able to offer this therapy several years before the first successful published use of ECMO in a neonate in 1975.\textsuperscript{29}

Dr Cornish, along with Drs Null and deLemos, did go on to establish the military’s first and only ECMO program at Wilford Hall in 1985. Wilford Hall was the 12th center to open in the United States and the first to open in Texas. Given Wilford Hall’s large catchment area and the existence of relatively few centers offering ECMO, candidates referred for ECMO were often moribund and too sick to safely transport by conventional means. This resulted in...
considerable morbidity and mortality during the referral process to include children dying either before or during attempted transport to ECMO centers. In an effort to address this problem, especially with regards to military dependents stationed with their families at bases where ECMO was not readily available, Drs Cornish, Null, and Neal Ackerman undertook studies to develop an ECMO transport system. During this process, they worked closely with the aeromedical research groups at Brooks AFB and spent many hours doing in-flight testing to ensure safety for the patient, equipment, crew, and aircraft. Their hard work led to the remarkably quick development of a safe and reliable ECMO transport system, resulting in the first ECMO transport being done by Wilford Hall shortly after the ECMO program opened. Figure 7 shows a picture of Dr Null with the original ECMO transport system.

Wilford Hall remains at present as one of the world leaders in ECMO transport capability, being 1 of only 3 centers in the United States that routinely performs regional ECMO transport and the only one with the technology and resources to routinely perform long-distance missions. The early Wilford Hall ECMO transport experience was initially described by Dr Cornish in 1990. Several updates of this experience have been additionally reported, with the most recent publication noting an average distance of 1380 miles per transport, including several transports from Okinawa, Japan, involving distances of >7500 miles (see Fig 8). To date, Wilford Hall has performed over 70 ECMO transports, including missions involving military dependents as well as civilian children requiring humanitarian rescue. All of these transports have been performed successfully and safely without the occurrence of a major complication. Given the high risk nature of ECMO transport, especially over extremely long distances often requiring multiple air and ground transfers, this accomplishment is truly remarkable. The success of the Wilford Hall ECMO transport program is a testament to the dedicated efforts of the many military neonatal nurses, respiratory therapists, and physicians who have been involved over the years, as well to the
commitment by the USAF Aeromedical System and Surgeon's General Office to make these missions happen.

Uniformed physicians stationed at Wilford Hall Air Force Medical Center and affiliated military institutions in San Antonio have provided many significant contributions to the field of neonatology. A test of the success of one’s research is often the impact it has on its clinical outcomes and longevity. Continuous flow ventilation is present in all neonatal ventilators today having been initiated by Drs Kirby and deLemos along with Jimmy Schultz. Doppler type blood pressure remains a mainstay in all newborn intensive care units. High frequency ventilation, thought by many to be a passing fancy, continues to be used for the very sickest patients from the smallest premature neonate to the largest adult. Wilford Hall remains as an innovator in ECMO research and extracorporeal support technology and continues to be one of the few centers in the world capable of providing ECMO transport to critically ill children.

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