THE HARTWELL FOUNDATION

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Linking Oxygen and Bacterial Ecology in Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is a devastating acquired inflammatory disease of the gut that affects about 2 out of every 1000 live births or about 6 to 7 percent of newborns weighing less than 1500g (3.25 lbs). It affects primarily premature infants that are at increased risk for acute and chronic impairments related to their immaturity, but may also occur in term and near-term babies. NEC accounts for substantial long-term morbidity in survivors of neonatal intensive care and is associated with significant mortality. It is a pathologic condition that develops quickly and without warning — inflammation within the intestinal wall spreads through the gastrointestinal tract, leading to gangrenous necrosis and destruction of the intestinal lining, bleeding, loss of intestinal function, and surgical intervention to remove the damaged tissue. NEC is second only to lung disease in causing infant death; over half of the babies that need surgery for NEC will die. Fortunately, early recognition and aggressive intervention improves clinical outcome and the use of human milk versus formula reduces the risk of NEC. As recent research suggests, resident bacterial communities in the gut (microbiota) seem to influence the course of the disease, where alterations in the composition of the microbiota may represent a signature of NEC. Yet, despite decades of scientific focus, the precise cause of NEC remains unknown. To address this unmet need, Lawrence proposes exploiting insights from a gut microbiota model called microbial ecology theory, which relates microbiota composition in the newborn gut to the adverse consequences resulting from a maldistribution of bacteria. For example, a microbial distribution that favors toxin-producing bacteria not countered by competing bacteria that oppose them creates an unhealthy microbiome. Specifically, he hypothesizes that the abnormally high levels of oxygen required for preterm infants to sustain life results in the persistent growth of oxygen-tolerant bacteria. Based on his preliminary evidence, he offers a new paradigm: when bacteria colonize sterile digestive tracts the level of gut oxygen decreases, whereas exposing healthy infant gut microbiota to elevated oxygen promotes NEC-like bacterial communities. To demonstrate this effect, he will track oxygen levels in mice during normal gut microbiota development and in laboratory bioreactors, where he can readily manipulate oxygen levels and characterize the changes that occur in cultured bacterial communities. If Lawrence is successful in establishing that elevated oxygen levels alter the gut microbiota in newborns and contributes to the development of NEC, he will provide new insights for intervention based upon a disease mechanism, which offers an alternative to empirical therapies. An effective therapy for NEC will reduce the morbidity and mortality of a disease that in its advanced stages kills half of all afflicted infants.