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Invited Commentary

Protecting the bowel of premature infants

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Necrotising enterocolitis (NEC) is a serious acquired gastrointestinal disease of the newborn, affecting 0·5–5 in 1000 live births[1], accounting for 2 % of neonatal intensive care unit admissions[2] and with a mortality rate ranging from 10 to 30 %[1]. Mortality is especially high in those neonates with perforated bowel requiring surgery. The disease is found particularly in premature infants and may be on the increase as a result of the increased survival of pre-term infants weighing < 1000 g. After birth, the intestine must adapt to a supply of enteral nutrients that are very different in composition from the amniotic fluid swallowed in the womb; it appears that the intestine of premature infants is frequently unable to adapt as effectively as that of term newborns. A cascade of events is initiated, which may ultimately result in the loss of intestinal barrier function, gut necrosis and gut perforation. Surgery is needed to remove gangrenous gut; thus, even if infants survive, they may be left with inadequate intestine to absorb the required nutrients and have a lifelong dependency on parenteral nutrition. It is very difficult to get premature infants to grow at rates equivalent to their growth rate *in utero*. Neonatologists are thus faced with a dilemma when feeding babies born prematurely – introduce enteral feeds very slowly, and accept suboptimal growth and all its consequences, or introduce enteral feeds more quickly in the hope of getting increased growth – but expose infants to the risk of NEC due to the lack of adaptation.

Although we understand some of the factors that may predispose to NEC, we are still far from a full understanding of how feed intolerance can ultimately have such catastrophic consequences, and therefore also of how to prevent the disease. The type of enteral feed given is important – breast milk is known to protect from NEC compared with formula feeds[3,4], and microbial colonisation/invasion also has an important role. Although various pathogens have been involved in NEC 'outbreaks', with *Clostridium* spp. and, more recently, *Enterobacter sakazakii* among the suspects[5,6], NEC is not simply an infectious disease of the gut.

NEC is a difficult disease to study clinically – the disease is extremely heterogeneous, it is difficult to study very sick premature infants, and what one measures in blood samples etc. may be the consequence of multisystem organ failure, rather than directly relating to the pathogenesis of gut failure. In order to understand more about the disease, Sangild *et al.*[7] have developed an elegant model of NEC in pre-term piglets which reproduces many of the features of the clinical disease, including a marked protective effect of the colostrum. In this issue of *The British Journal of Nutrition*, they provide some very provocative data obtained using this model[8]. Their starting hypothesis was that intra-amniotic lipopolysaccharide (LPS) administration would decrease sensitivity to NEC, with the rationale that prenatal exposure of the fetus to LPS would accelerate gut maturation and improve bacterial tolerance. Intra-amniotic LPS exposure (with postnatal formula feeding) not only decreased the severity of NEC compared with formula-fed piglets, so that it was intermediate between that of formula-fed pigs and colostrum-fed pigs, but also resulted in improved villus height, enzyme activities and intestinal permeability compared with formula-fed piglets. These observations lead to many more questions than answers, and intra-amniotic LPS administration is obviously not viable as a clinically useful tool to decrease NEC incidence. However, a further exploration of the mechanisms involved here could ultimately yield what is so badly needed in NEC, either a way of preventing the disease or of treating it. The authors hypothesise that intra-amniotic LPS induces a state of immune tolerance via differential regulation of a number of genes. However, another intriguing aspect of their data is the increased villus height and the activity of digestive enzymes in piglets that received intra-amniotic LPS. The intestinal epithelium is usually an area of very rapid cell division and migration, with cells constantly being shed from the villi into the lumen and being replaced by new cells from the crypts. Recently, a cryptal stem cell niche has been identified that expresses *lgr5*, and it appears to be these cells that are responsible for regeneration[9]. Crucially, NEC is not only a disease in which epithelia are damaged, but also a disease in which epithelial regeneration is impaired, presumably mediated via some effect at, or damage to, the *lgr5* stem cell population. This epithelial regeneration can also be impaired by the activation of toll-like receptor 4 (TLR4), which is activated by LPS[10,11]. Should not intra-amniotic administration of LPS therefore cause TLR4 activation, impaired epithelial restitution and an increase in NEC severity, rather than the decrease observed by Cilieborg *et al.*? There is much contradictory data on TLR4 activation in the intestine, as highlighted recently[10], but it is possible that pre-term activation of TLR4 may produce a state of tolerance, in which the subsequent responsiveness to TLR4 activators is impaired. The relationship between TLR4-responsive cells and *lgr5*-positive cells in the intestine is not currently known, but an understanding of

this axis may ultimately lead to the prevention and treatment of NEC and could also be very useful for therapy of other inflammatory bowel conditions.

There are no conflicts of interest.

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