tion. Paludetto *et al*. concluded that the poorer neurological performance of the jaundiced infants ($n = 12$) at 1 month could be the result of the jaundice itself or the phototherapy.

In order to be able to answer the critical questions raised, further research on the effect and management of moderate degrees of hyperbilirubinemia in full-term infants is urgently needed.

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To the Editor: The review article ‘Antioxidants as Therapy in the Newborn: Some Words of Caution‘ by Jankov, Negus, and Tanswell (1) is both timely and thought provoking. The concept that debilitating sequelae of premature birth may be due to oxygen radical disease was first hypothesized by Saugstad in 1988 (2). This model, as a possible unifying paradigm, was attractive because so many debilitating diseases might be prevented by dealing with a single cause, the inability of the premature newborn to cope with oxygen. This hypothesis is even more attractive because the ‘treatment‘ may very well be the administration of compounds whose structure and metabolism is well known.

The strength of this review article is that it forces us to pause and consider what we are attempting to do with antioxidant therapy since, as the authors state, ‘it remains unknown which radicals mediate injury, which oxidation products have roles in disease, and which cellular components are most susceptible, in specific disease entities of the newborn‘. They point out the ‘good‘ side of free radicals in cell signaling and caution against potential deleterious side effects of antioxidant intervention.

It is here where I wish to present a different perspective. There have been multiple studies of single antioxidant interventions in the premature, albeit with mixed results. There may be a need to use mixtures of antioxidants or cocktails and in order to cover a variety of cells and subcellular compartments in order to treat the total system. An example is the use of vitamin C (water soluble antioxidant) and vitamin E (lipid soluble antioxidant) which together appear to interact at the cell membrane and function in ways that neither could do alone (3, 4). Indeed, as we have reported for the antioxidant properties of human milk, it may not be individual components at all but entire systems with unique properties of their own that provide protection (5).

In reference to the ‘good‘ side of free radicals, the authors eloquently describe that role. However, this perspective is more appropriate for the healthy normal infant not for the premature infant whose lungs and other organs are exposed to oxygen, itself a free radical, before development has provided the tools to cope. It is the imbalance of uncontrolled overexposure to oxygen and under development of the natural antioxidant defense that creates a new problem that we may be able to assist with exogenous antioxidant intervention. Analogies are the use of lung surfactant to ‘prop up‘ the immature lung in oxygen uptake and gas exchange.

With the advent of technology that has increased the survival rate of the premature, we have brought into existence a new subset of the human population who would normally not need to cope with oxygen (both too little and then too much), unprepared, with inadequate tools. To wait, as the authors suggest, to fully understand the ‘ROS or RNS involved, the site of injury, and the biologic molecule to be protected‘ before attempting antioxidant therapy is sensible but not practical. I believe there is enough evidence now to consider trials with antioxidants. In the area of birth defects, there has been a dramatic drop in neural tube defects across North America that has occurred since fortification of flour with folic acid. We still do not know if the neural tube doesn’t close, re-opens or even how folate performs at the molecular level. If we had waited to fortify until we completely understood the process, there would be many more children in wheelchairs right now.

We believe that early intervention with antioxidants may benefit the premature infant (6). We are in the process of designing an animal model study to test that hypothesis. We also have, in progress, a trial in enterally fed premature infants to boost glutathione reserves.

At some point after risk/benefit assessment, and a considered appraisal of available data, a leap of faith is required no different than the first time lung surfactant, dexamethasone, erythropoietin or antibiotics were used to improve outcome. Some worked, some didn’t, and none were free of side effects. This is how we progress, and indeed how we have arrived at present treatment modalities for the low birth weight infant.

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Response

To the Editor: We thank Dr. Friel for his kind introductory remarks regarding our review article "Antioxidants as Therapy in the Newborn: Some Words of Caution" (1), and take no great issue with his other comments. As reflected in the title of our review, our intent was to introduce a note of caution, not prohibition. Our laboratory has a long history of studying antioxidant interventions in animal and cell culture models, with the ultimate hope that the collective data and advances from such models will allow that "leap of faith" to studies in human infants. Indeed, as Dr. Friel has pointed out, several groups have already taken such a leap. It was just this increase in human studies of antioxidants that stimulated us to write our review. We believed, rightly or wrongly, that there was a widespread, if understandable, lack of awareness by physicians of the important physiological roles played by reactive oxygen species, and the potential consequences of antioxidant interventions. One could equally posit that there is an equivalent lack of awareness of the capacity of many antioxidants to act as pro-oxidants. This is not to say that clinical trials of antioxidants should not happen: they should. They should not, however, happen without the investigators involved being as fully informed as possible of potential adverse affects.

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