Immune depression in the malnourished child: Knowledge all dressed up with nowhere to go

Nearly one million children under five years of age die annually from wasting deficits of protein and energy acting in synergy with pneumonia and diarrhea, and this toll is undoubtedly exceeded numerically by an additional burden of infection-related morbidity. Prevention is obviously the preferable response to this disaster, but clinical management strategies will be required into the indefinite future. To facilitate effective therapeutic interventions, however, particularly for the most debilitated patients, a sophisticated understanding is needed of malnutrition-associated susceptibility to infection.

For sixty years immune depression has been explored, and increasingly accepted, as a decisive link between childhood malnutrition and susceptibility to infection, and a large catalog of information has accrued describing the immune responses of malnourished children. Improvements in clinical management over this period, however, have been achieved largely independently of this knowledge base which, for all practical purposes, lies fallow. The field is adrift, clinging to a simplistic unifying paradigm of chaotic immunological attrition that can confer neither form nor direction to its accumulated knowledge. Arguably this is attributable, in significant measure, to prevailing doubts within the field regarding the relevance of animal-based experimentation and to consequent inattention to a body of animal-based findings pointing to a much needed paradigm shift. The opinion paper considered here identifies reasons for this skepticism together with necessary and realistic improvements to animal models of the inflammatory immune depression associated with acute childhood malnutrition.

Intellectual neglect in modeling has been prevalent. It is astonishing how frequently animal models have failed to duplicate critical features of childhood malnutrition pathology because priority has been placed, instead, on reproducing human dietary minutiae. Likewise, animal models have rarely reflected deliberate and rigorous selection of a developmental stage corresponding to a targeted stage of childhood development. For example, a popular suckling rat model is relevant only to stages of human immunological development that are completed in the womb. Moreover, differences between the immune defences of humans and animals are critical to the relevance of a model employing conventional animals, but this decisive factor has generally escaped consideration.

Some shortcomings associated with conventional experimental animals can be largely overcome by means of newer tools not yet applied to investigations of malnutrition-associated immune depression. For example, much reasonable concern centres on the limited genetic diversity of conventional experimental animals when compared to the diversity within and among human populations. However, mouse stocks are now available exhibiting genetic heterogeneity comparable to that of human populations. As a second example, the “humanized” mouse carries and expresses bone marrow-derived components of the human immune system in place of the

corresponding murine components, thereby permitting invasive studies of many human immune defences in vivo.

Despite a pervasively laissez-faire approach to animal modeling, a nucleus of animal-based investigations has escaped the worst design pitfalls and yields insights unavailable from studies of humans. Most importantly, some of this work points to a proposition, the antithesis of the prevailing notion of uncontrolled immunological degradation, centred on sustained regulation of immune functions in the face of deepening malnutrition. In this proposition, dubbed the Tolerance Model, a regulated shift emphasizing non-inflammatory immune functions is proposed to reduce the risk of autoimmune pathologies in a flood of wasting-associated self antigens. Substantial fundamental and clinical implications follow and, if pursued using intellectually rigorous modeling together with the newer animal-based tools identified herein, the proposition could emerge as a unifying paradigm to revive the field.

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Publication

Fidelity in Animal Modeling: Prerequisite for a Mechanistic Research Front Relevant to the Inflammatory Incompetence of Acute Pediatric Malnutrition.
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