Invited commentary

The thymus: a barometer of malnutrition

In 1810 J. F. Menkel noted that the human thymus was especially sensitive to malnutrition (see Jackson, 1925; Beisel, 1992), and the term 'nutritional thymectomy' came into common usage. By 1845 Simon (1845) had observed that the thymus is 'a barometer of malnutrition, and a very sensitive one'. These observations were made over a century before the role of the thymus in lymphocyte development was truly understood. In this issue, Malpuech-Brugère *et al*. (1999) add a new paragraph to the story by showing that thymic involution in Mg-deficient rats starts with enhanced apoptosis occurring within 2 d of receiving a Mg-depleted diet (Malpuech-Brugère *et al*. 1999). They suggest that this may be the result of an increased sensitivity to oxidative stress which may in turn be a mediator in the apoptotic process (Vaux & Strasser, 1996). Whether or not this is the case, and whether we should be surprised that thymic involution may be a carefully managed process in which cells are selectively culled, is open to debate, but there are wider aspects which are also interesting.

We have recently passed through an era in which the thymus has been treated with cavalier disdain by some physicians who believe it to be a vestigial remnant after it has fulfilled its initial function in early lymphocyte selection. Large thymuses appearing on children's chest X-rays were intentionally reduced by high-dose irradiation and many cardiac surgeons still routinely excise the thymus during open heart surgery. The immediate effects of these procedures seem surprisingly benign (Brearley *et al*. 1987), at least in modern societies with low levels of infectious disease. However, there has been very little long-term follow-up, and many immunologists are now concluding that we may have underestimated the importance of thymic function in both early and later life. For instance, in the children of HIV-infected mothers, those showing evidence of a thymic defect are much more likely to become HIV-positive, and to succumb more rapidly to AIDS (Kourtis *et al*. 1996). It has also been shown that an active thymus promotes T-cell replenishment in adults following intensive chemotherapy (Mackall *et al*. 1995).

The life-course of the human thymus starts with very early embryonic development (with functional T-cells detectable by 12 weeks gestation) and rapid growth in the fetus. Growth continues postnatally until adolescence when there is a gradual atrophy and infiltration by fatty tissue. In neonatal mice, surgical thymectomy on day 1 is fatal, but on day 7 is only associated with modest excess mortality under conditions of captivity. Thymectomy on day 2 has a quite different effect, leading to auto-immune disease in susceptible strains. Thus the timing of thymic damage is critical to long-term prognosis. Our own interest in this topic has arisen from an observation that rural Gambian people who were born during the annual hungry season are over ten times more likely to die from infectious diseases as young adults than those born in the harvest season (Moore *et al*. 1997). We have speculated that this could represent a programming of immunity following early nutritional damage to the thymus (Prentice *et al*. 1999).

It seems to be a universal observation that nutritional deprivation, in its many forms, has a proportionately greater impact on the size of lymphoid tissues, particularly the thymus, than on other organs (Prentice *et al*. 1999). This is especially true during fetal growth. Considerable work has been done in both man and other animals on the impact of protein–energy malnutrition (e.g. Golden *et al*. 1977), and on Zn (e.g. Beach *et al*. 1980) in relation to thymic development. Much of this has used the simple outcome measure of thymic size, though some of the human studies have looked at cell-mediated immunity (Ferguson *et al*. 1974; Ferguson, 1978), and some animal studies have looked at survival rates following prenatal and postnatal Zn depletion (Beach *et al*. 1980). Measures of thymic size appear to be useful in young human subjects and reveal, for instance, that breast-fed infants have thymuses on average twice the size of those in formula-fed infants (Hasselbalch *et al*. 1995), and that thymic size at 3 months of age is a powerful predictor of infant mortality in a developing country setting (P Aaby, personal communication). However, size alone is only the crudest of measures. Examination of electron micrographs of the thymic medulla reveals an exquisite pattern of microstructures and countercurrent microvasculature designed to host the developing lymphocyte and to allow for both positive and negative clonal selection (Boyd *et al*. 1993). In terms of its fine microstructure the thymic cortex and medulla are somewhat analogous to the kidney in which nutritional deprivation in fetal life has been shown to cause large and permanent decreases in vascular and nephron density (Mackenzie & Brenner, 1995; Rensens *et al*. 1997). Though the issue has not yet been researched, it seems highly likely that the apoptotic involution in response to Mg deficiency described by Malpuech-Brugère *et al*. (1999), and to other deficiencies, will have an impact on the delicate microstructure of the thymus, and in this way could 'hard wire' the effects of these early insults and lead to permanent programming.

Just as thymic size is only a crude index of function, T-cell number and various tests of cell-mediated immunity are also crude measures of protection. Circulating T-cell levels are homeostatically regulated and hence often maintained, or even elevated, in sick and malnourished children. This may mask defective function (Ferguson *et al*. 1974; Ferguson, 1978), or a critical hole in the T-cell repertoire caused by defective clonal selection in a malnourished

thymus. Alternatively, the negative selection of auto-reactive lymphocytes might be impaired since 95% of thymocytes (those which have become activated to benign antigens) are destroyed in the thymus, and failure to do so results in a breakdown in immune tolerance and to auto-immune disease. The thymic microstructure is vital to the development of tolerance (Mackay & Gershwin, 1997; Takeoka *et al*. 1997), so early nutritional deficiencies could play a role in causation of auto-immune disease and there is preliminary evidence to support this idea (Phillips *et al*. 1993; Godfrey *et al*. 1994). In passing, it is noteworthy that the elimination of auto-reactive T-cells is another example of a carefully regulated apoptosis (or activation-induced cell death) which is mediated by Fas 'death' receptors and their ligand (Brunner & Mueller, 1999).

The observation that the thymus is always the most vulnerable organ to nutritional stress fits with the observation of Malpuech-Brugère *et al*. (1999) that its atrophy represents an ordered process controlled by the induction of apoptosis. Personally, I doubt whether it is an accidental result of increased susceptibility to oxidative stress as suggested by the authors. It seems more likely that a mechanism has evolved for prioritizing organ maintenance under conditions of starvation. Aquired immunity (for which the thymus is essential) creates prospective defences against a second invasion by a micro-organism that has previously been encountered, and as such can be considered less essential than innate immunity. The organism can gamble that it will not be subjected to potentially fatal infections, whereas loss of many other organ functions would lead rapidly to death. In a similar way it is known that thymic size reduces markedly within hours of certain stresses (e.g. infection, acute starvation or glucocorticoid administration) (Clarke & MacLennan, 1986). It appears that the lymphocyte foot soldiers flood out of their training camp, and that square bashing in the thymus is put on hold until the invasion is quelled. In other words thymic function can be switched on and off according to other priorities.

An important aspect of the Malpuech-Brugère *et al*. (1999) paper is that they pair-fed the Mg-replete controls to account for possible decreases in food intake in the deficient animals. This should overcome any protein–energy-mediated effects which elsewhere have been shown to be critical in respect of leptin and its actions on the immune system. The exciting finding that leptin stimulates *in vitro* measures of aquired immunity through receptor-mediated actions on T-lymphocytes was published last year (Lord *et al*. 1998). The same team will soon publish some remarkable results concerning leptin's role in mediating thymic atrophy during modest food restriction. One of the key findings is that tissue atrophy and lymphocyte depletion occur in a highly selective, and hence managed, manner. This strengthens the view that tissue depletion in malnutrition does not occur through the random death of the most vulnerable cells, but rather as a highly organized process of closing down functions which can be best sacrificed in the short term in order to ensure long-term survival. The success of this strategy can be seen in the millions of survivors of severe fetal or childhood malnutrition, but the system is not perfect and they bear the long-term scars. A better understanding of the inter-relationship between nutritional deficiency and apoptotic processes may help to clarify some of the long-term effects of malnutrition which have become of such interest in recent years.

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