Endocrines in protein–energy malnutrition

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With the availability of radioimmunoassay methods for measuring hormones in biological fluids, there have been a growing number of publications on the plasma or serum concentrations of hormones in severe protein-energy malnutrition (PEM). It is not so easy, however, to interpret the meaning of many of these measurements. Some endocrine abnormalities only appear in severe malnutrition and are a product of the final pathology. Other changes occur much earlier and may influence the pathogenesis of PEM, particularly which of the different forms—kwashiorkor or marasmus—ultimately materializes.

It is also important, in reviewing endocrine information in malnutrition, to recognize that diet is only one environmental factor which may determine the endocrine status of the individual. Most children who are potentially at risk to PEM are subjected to a wide range of adverse environmental circumstances and their over-all endocrine balance will be the net product of the interaction of these events.

In this short review I will first summarize the basic endocrine pattern found in the severe condition. Then I will look at those changes which may have been important in the emergence of different types of protein–energy malnutrition.

Endocrine changes in severe PEM

Insulin. Most studies have reported low fasting levels of plasma insulin in PEM, regardless of whether one is dealing with kwashiorkor, marasmus or marasmic kwashiorkor. An impaired glucose tolerance and a reduced or absent insulin response to glucose have also been demonstrated by various authors in children with kwashiorkor.

It is not particularly clear why children with PEM should exhibit low fasting levels of insulin. The most obvious suggestion would be low food intake. Earlier workers also drew attention to the fact that there was frequently pancreatic atrophy (Davies, 1948), but this has been disputed by Pimstone *et al.* (1973). The latter group have suggested that it might be β cell damage which leads to poor insulin secretion and impaired glucose tolerance in severe PEM and have linked this to the state of potassium depletion of their children; potassium supplementation certainly seemed to improve glucose tolerance.

A deficiency of chromium has also been implicated in the aetiology of reduced insulin activity. Chromium is a component of glucose tolerance factor and small amounts of chromium, when administered in nanogram amounts as glucose

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tolerance factor, did improve glucose tolerance in Jordanian children (Hopkins & Majaj, 1967).

Cortisol. Early studies on adrenal function in severe PEM were based on urinary steroid excretion and indicated hypo-function (Trowell *et al.* 1954; Baig & Edozien, 1965). It is likely, however, that these investigations were probably misleading and the majority of more recent measurements on cortisol status agree with the findings of Alleyne & Young (1967) that plasma cortisol concentrations are elevated in PEM, particularly when there is a high degree of wasting. A multiplicity of factors contribute to the elevated plasma cortisol levels in severe PEM, but the two most important ones are probably stress—especially that due to infection (Lunn *et al.* 1973)—and hypoglycaemia (Alleyne & Young, 1967).

Growth hormone. Reports concerning the plasma levels of growth hormone in severe PEM are frequently conflicting and it would appear that concentrations may be different in kwashiorkor and marasmus. Various workers have demonstrated a significant negative correlation between plasma growth hormone concentrations and the corresponding levels of plasma albumin. Thus very low plasma albumin concentrations, of the type one would expect to find in severe kwashiorkor, are associated with high plasma growth hormone concentrations. The magnitude of the growth hormone concentrations in severe kwashiorkor can be very high indeed, 60 ng/ml, and fall into the range of values quoted for acromegaly (Lunn *et al.* 1973).

The causes of the high growth hormone concentrations in kwashiorkor are by no means completely understood. The longitudinal study described by Lunn *et al.* (1973) in children living in an area where kwashiorkor was endemic indicated that elevated growth hormone concentrations occur only late during the development of kwashiorkor. Thus it has been concluded that elevated growth hormone concentrations have little effect on the early stages of pathogenesis.

The original suggestion of Kernoff *et al.* (1971) that growth hormone concentrations might be related to the size of the intravascular albumin pool has been difficult to substantiate. It has also been reasoned that the high growth hormone concentrations might be associated with hypoglycaemia, but Pimstone *et al.* (1968) failed to demonstrate any effect of glucose infusion on growth hormone concentration. It has also been suggested (Pimstone *et al.* 1973) that plasma growth hormone concentrations appeared to be correlated with plasma alanine and branched chain amino acid concentrations. The increased growth hormone concentrations might be linked to the low levels of somatomedin which have been reported in severe kwashiorkor (Grant *et al.* 1973). Most growth-promoting properties of human growth hormone are mediated via somatomedin and the high levels of the growth hormone might be present because of a failure of somatomedin release from the liver.

Other hormones. Studies on other hormones are less complete and will not be discussed here. They have been reviewed in a symposium of the Kroc Foundation (1973).

Hormonal status and the pathogenesis of PEM

Various groups of workers have attempted to show that some of the hormonal changes discussed above might be intimately involved in the actual pathogenesis of PEM, particularly the cortisol abnormalities.

Towards the end of the 1960s evidence began to emerge which suggested that kwashiorkor and marasmus could not be explained simply on the basis of differences in dietary protein intake. Epidemiological studies from India, and subsequently from other parts of the world, failed to show any difference in the average ratio protein:energy of the diet customarily consumed in areas where kwashiorkor predominated, as opposed to marasmus. Gopalan (1968) introduced a new concept. He suggested that kwashiorkor was not usually the specific result of protein deficiency but was essentially a failure of adaptation. He proposed that the biochemical mechanisms which are usually invoked to protect nutrient supplies to essential tissues like the liver, at the expense of muscle, during food shortage fail to operate. He said that this was why abnormalities of liver metabolism tended to predominate and ultimately why the child would be prone to kwashiorkor rather than marasmus.

Subsequent studies from Hyderabad indicated that plasma cortisol levels in kwashiorkor were not elevated to anything like the same extent in children with marasmus, and it was suggested that this might be the result of an inadequate adrenal response. Rao (1974) for example, in studies on hospitalized children with severe PEM, observed that cortisol concentrations were much lower in cases of kwashiorkor with intercurrent infection than in cases of marasmus with the same degree of infection.

The basic idea which evolved from these studies was that if muscle wastes in an under-nourished child under the influence of cortisol, it will result in the liver being provided with a supply of amino acids not only for gluconeogenesis, but also for liver protein synthesis. Thus, in spite of an over-all deficiency of dietary protein, the liver's supplies of amino acids would be buffered by muscle breakdown, minimizing any reduction in the synthesis by the liver of important proteins for homoeostasis, like albumin.

If, however, this plasma cortisol response failed, then the liver would not be protected in this way against an inadequate protein supply. Plasma albumin concentrations would then fall rapidly and kwashiorkor would emerge.

It is difficult, however, and in some circumstances quite misleading, to assume that biochemical differences observed in the severely malnourished child in hospital are in any way relevant to what has been happening during the actual pathogenesis of the disorder. This was one of the reasons why the emphasis of our own research into PEM moved away from severe kwashiorkor and marasmus in the ward towards outpatient or under-five clinics, where we had access to children who were at risk to different forms of PEM but were not suffering from the severe disorder. The work I am going to describe was carried out as part of two prospective longitudinal studies designed to investigate the wider ecology of PEM

in two different settings, one in a village called Namulonge, in Uganda, where kwashiorkor predominated, and the other in Keneba, The Gambia, where marasmus is the main type of PEM. A multiplicity of environmental and clinical measurements were made, but I will only describe those which are relevant to the present topic. The children of both villages were followed prospectively from 0–3 years of age. They were under the continual care of a qualified paediatrician and a community nurse and received all appropriate therapies required, both dietary and chemotherapeutic.

The growth and general development of the children in these two communities was quite different from an early age. Fig. 1 shows what happened to the weights of the children relative to the standards of Stuart & Stevenson (1954) as modified by Jelliffe (1966). Weight gain was much more severely retarded in The Gambia than in Uganda, as was height gain, development of subcutaneous fat and muscle (Whitehead *et al.* 1977). The anthropometric differences between the two countries contrasted, however, with corresponding changes in plasma albumin

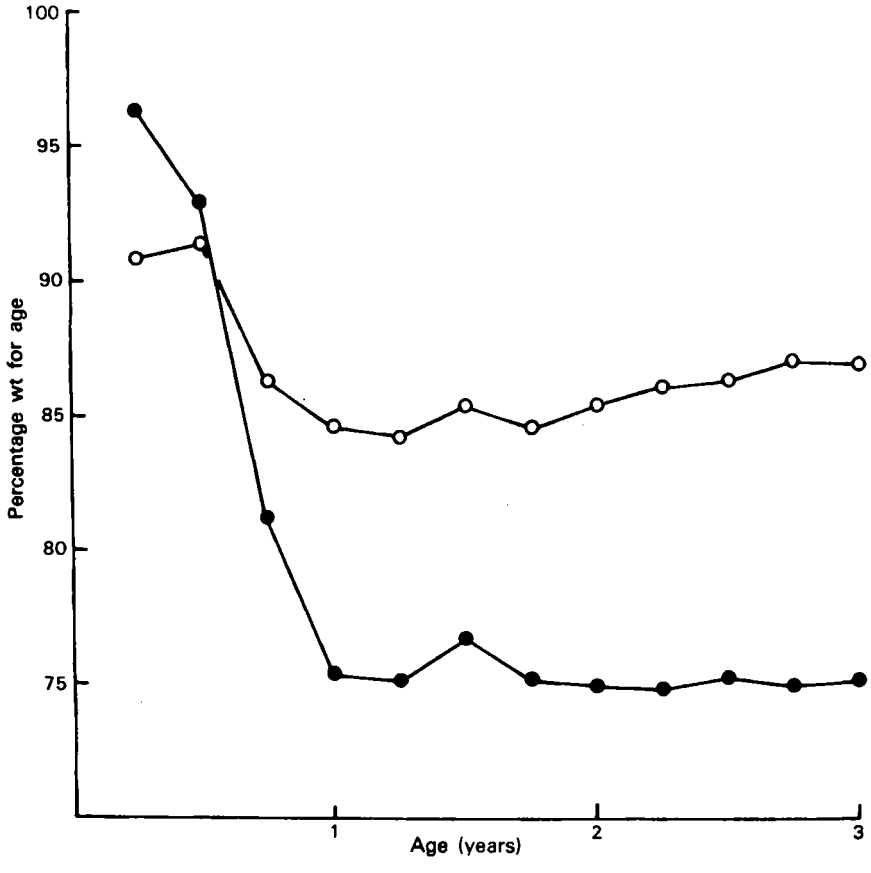

Fig. 1. Growth in weight of Ugandan and Gambian children relative to the international standard (Jelliffe, 1966). (●), Gambia; (○), Uganda.

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concentration. In The Gambia plasma albumin concentrations were maintained at much higher levels than in Uganda, where in fact albumin concentrations were progressively falling from around six months of age. The differences in patterns of growth and changes in plasma albumin concentrations between these two communities clearly started to appear at an early age and were of a type likely to pre-empt the sort of malnutrition which might emerge in the second and third years of life.

Were these different growth and albumin patterns associated with demonstrable differences in hormonal background? Figs. 2 and 3 show the corresponding plasma

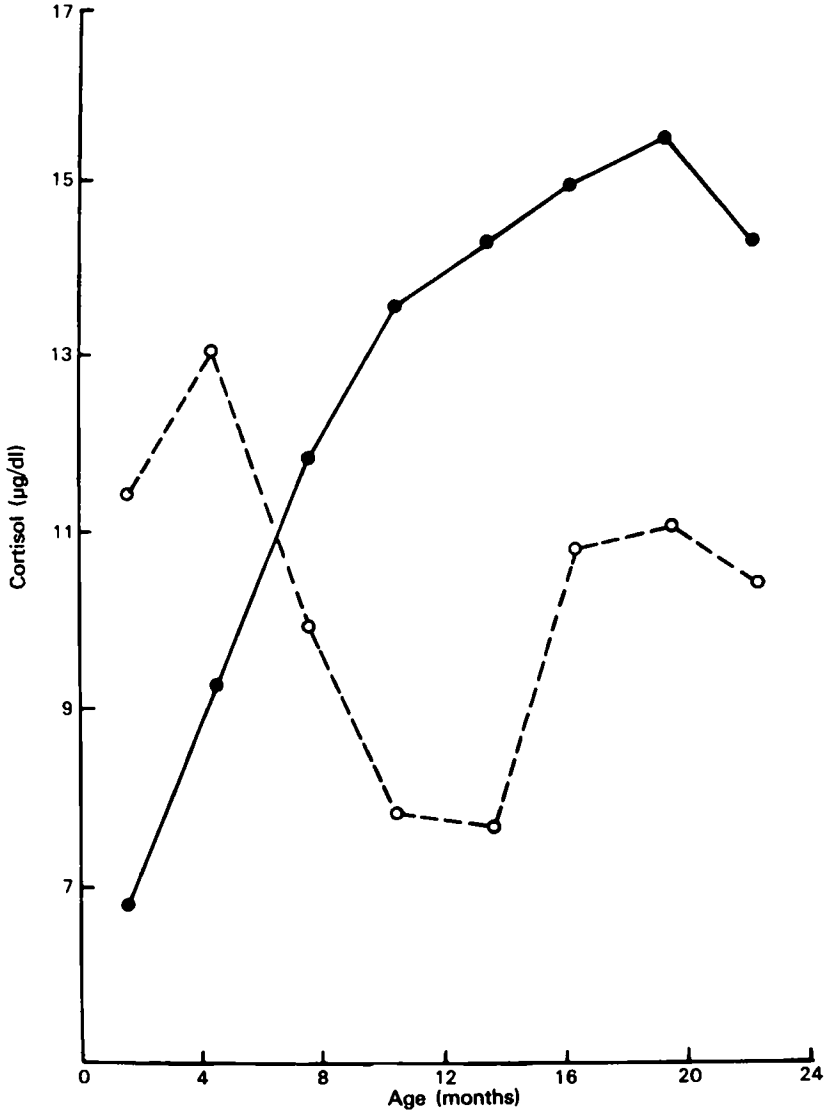

Fig. 2. Plasma cortisol concentrations in Ugandan and Gambian village children at different ages. (●), Gambia; (○), Uganda.

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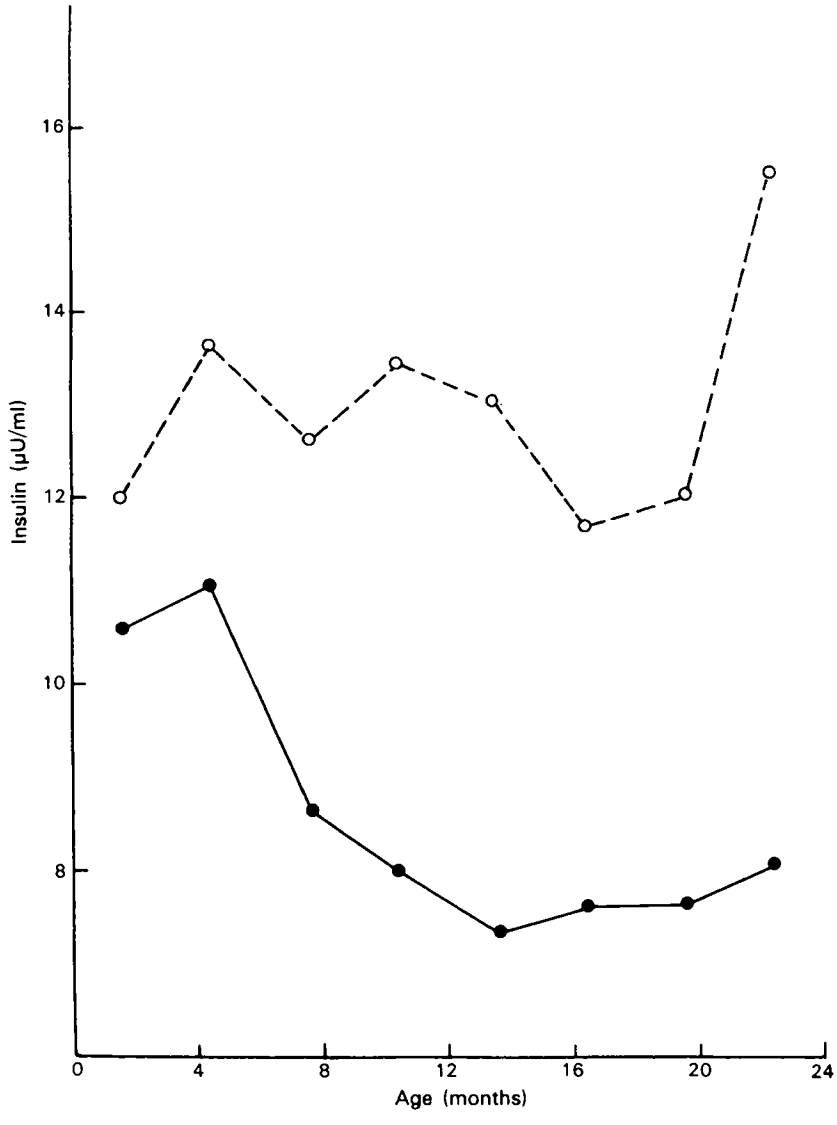

Fig. 3. Plasma insulin concentrations in Ugandan and Gambian village children at different ages. (●), Gambia; (○), Uganda.

cortisol and insulin values. In The Gambia it is apparent that plasma cortisol concentrations became consistently higher, and insulin concentrations consistently lower, than in Uganda.

From a metabolic point of view it is probable that the higher insulin concentrations in Uganda were equally as important as the higher cortisol concentrations in The Gambia to the aetiology of the predominating forms of PEM. Higher insulin concentrations are known to promote the movement of amino

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acids towards muscle as opposed to liver; just the opposite effect of cortisol. This would remove even more the protective effect normally afforded to the liver during the development of the marasmic type of PEM. The fact that the distribution of free amino acids between muscle and liver is affected when the hormonal background is altered has been demonstrated in a series of investigations on experimentally malnourished rats (Lunn *et al.* 1976). It was demonstrated quite conclusively that low liver amino acid concentrations, a low liver protein content, and reduced plasma albumin concentrations which arise from the feeding of low protein-containing diets can all be reversed by the administration of cortisol, even although dietary intake is unaffected.

The results I have produced do provide strong evidence to support the concept that the two major types of PEM might emerge from different hormonal backgrounds, backgrounds which are established at an early stage during the life of the child. The question is, what is the reason for these hormonal differences?

The suggestion of Rao (1974) that kwashiorkor might result from an actual failure of the adrenals can be ruled out in the present circumstances. Although cortisol concentrations were consistently lower in Uganda, when the children were infected plasma cortisol concentrations did become elevated, and this was just as true in the children subclinically malnourished as in severe kwashiorkor. It is still possible, however, that infection may be linked with the cortisol differences. It has been shown (Cole & Parkin, 1977) that the children in The Gambia were affected by infection much more than those in Uganda. This was particularly the case with diarrhoeal disease, and the severe dietary energy deficit and tendency towards hypoglycaemia arising from the diarrhoea and vomiting would be an obvious stimulus for cortisol concentrations to become increased.

The reasons for the differences in plasma insulin concentrations in The Gambia and Uganda also need to be explained. There is, however, always a tendency for insulin and cortisol concentrations to respond in a reciprocal manner and it is possible that the opposite response of these two hormones has a common cause. Alternatively, other factors such as potassium or chromium deficiency could be implicated, but we have not examined these possibilities.

Clearly we are not in a position to provide anything like a complete explanation for the different aetiologies of these two types of protein–energy malnutrition, but it seems to us possible that when a child has insufficient to eat, exactly which organ is affected the most is affected by the over-all hormonal status of the child. One factor which can affect this hormonal pattern is the balance between protein and carbohydrate in the diet and this could be why kwashiorkor does tend to predominate in countries where the basic staple has a particularly low protein content. But protein and energy deficiencies are only one factor: a disease like diarrhoeal disease could completely overwhelm the hormonal and metabolic response that one would expect from the diet alone. Whether or not kwashiorkor or marasmus emerges in a community probably is determined by the complex interactions between the nutritional composition of the diet, total energy intake and the range of environmental stresses to which each child is exposed.

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