Metabolic Effects of Malnutrition in Childhood

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Children may respond biochemically to nutritional stress in three main directions. There may be an altered rate of chemical development, a change in body composition, or an adjustment in the activity of individual metabolic processes; in many instances a combination of these changes is found.

Clinically, the importance of these responses lies in their functional sequelae, their empirical influence on prognosis, and whether they are reversible. Biologically, however, it may be the evolution of these changes that claims most attention. Do they reflect an intrinsic change in the metabolic system or are they merely some peripheral evidence of a sick cell? Are they a successful adaptation to an altered nutritional environment or do they imply nutritional failure?

NUTRITIONAL ADAPTATION AND FAILURE

Although Dr Waterlow touched on it in his Charles West Lecture (Waterlow, 1968a), the concept of nutritional failure as opposed to adaptation is a relatively new one. Clinically, however, we are used to distinguishing between adaptation of the myocardium to (say) a mitral stenosis, and its eventual breakdown into heart failure, and it seems probable that similar concepts could be applied to nutrition. Heart failure is an interesting example and may be looked at in nutritional terms. Ugandan children with kwashiorkor were liable to develop cardiac failure if the haemoglobin was below 7 g/100 ml and if the dietary intake of sodium was much more than 1 mEq/kg (Wharton et al., 1967). In the majority, the myocardium adapted to, or compensated for, these nutritional stresses with an increase in size, visible on X-ray, and an increased left ventricular activity (Wharton et al., 1968), but in 10 per cent adaptation was unsuccessful and frank heart failure eventually occurred. Apart from anaemia and fluid retention as a cause of heart failure, there is also histological and biochemical evidence of a myocardial lesion in kwashiorkor, e.g. the plasma level of the first band of the lactate dehydrogenase (LDH1) isoenzymes is above normal in about half of the children with kwashiorkor before treatment, improving rapidly with nutritional repletion. These increased LDH1 levels presumably indicated dead or dying cells, which seems good evidence of nutritional failure. Since frank heart failure occurred in only 10 per cent it is
clear that the concept of nutritional failure, if it exists, does not necessarily coincide with the syndromes of organ failure that we are used to diagnosing clinically.

CHANGES IN CHEMICAL DEVELOPMENT
An essential sign of malnutrition in childhood is growth failure, a sign which by its nature is limited to the developing organism. In chemical terms the alterations in growth and growth velocity during malnutrition are closely related to changes in total hydroxyproline excretion. Figure 1 shows the origin and fate of hydroxyproline in the body; its excretion reflects the turnover

Fig. 1. Hydroxyproline metabolism. Most of the hydroxyproline appearing in the urine is in the peptide form; it is being made by fibroblast that comes ultimately from a soluble collagen pool.
rate of the collagen containing tissues and there is a wealth of evidence to relate this to growth velocity. Therefore, since malnourished children are not growing, their hydroxyproline excretion is below normal, increasing rapidly with treatment (Whitehead, 1965; Howells et al., 1967). Similarly, hydroxyproline in the amniotic fluid of those pregnancies producing ‘small for dates’ babies is well below that found in pregnancies producing normally grown ones (Wharton et al., 1971). This relationship between hydroxyproline excretion and growth does not hold completely true. For example, some children with kwashiorkor have a high excretion of hydroxyproline and these children have a mortality rate about five times as high as those with the expected low excretion (Howells et al., 1967). Furthermore, although some children with coeliac disease have an appropriately low excretion which rises promptly when a gluten-free diet is instituted, in others, despite marked growth failure, the excretion is high, falling a little with treatment (Wharton and Pennoock, unpublished). In adults with coeliac disease the high excretion of hydroxyproline is thought to represent osteomalacia (Crabbé and Isselbacher, 1965) and it is probably this mechanism that accounts for the occasionally high excretion in children with coeliac disease or kwashiorkor. It could be argued therefore, that a low hydroxyproline excretion (because it is associated only with a reduction in growth rate) reflects adaptation, while an increased excretion (associated as it is with tissue breakdown and an increased mortality) indicates nutritional failure. More speculatively, one wonders whether a high hydroxyproline excretion in the presence of under-nutrition indicates that the organism is ‘trying’ to grow inappropriately for its nutritional environment, so indicating a complete lack of adaptation.

ALTERATIONS OF BODY COMPOSITION

There are many studies of body composition in malnutrition, ranging from the classical clinical analysis of cadavers in Germany during the last century to the modern dilution techniques. Garrow et al. (1968) have reviewed this subject, but two aspects, the water and protein content of the body, will be discussed here.

Water

All malnourished children, whether oedematous or not have an increased body water, the greater the weight deficit the greater being the proportion of body water (Brock and Hansen, 1965); since younger animals have a greater proportion of body water than mature ones (Widdowson, 1964) it seems that the malnourished child shows a form of developmental regression. Similarly, children born at term with severe intrauterine growth retardation have a
larger extracellular fluid volume than normally grown ones, and one which is more appropriate for a fetus of 34 weeks' maturity (Cassady, 1970). Whether the onset is intrauterine or postnatal, these marasmic children, despite their increased body water, may appear clinically 'dehydrated' because of their lax subcutaneous tissue. Such children presenting with gastroenteritis or pyloric stenosis frequently have a greater body water than our clinical acumen suggests, and this may lead to 'over-dripping', over-hydration and a risk of pulmonary oedema.

A further clinical point concerning body water is shown in Table 1 which defines kwashiorkor, marasmic kwashiorkor, and marasmus. Since both the child with marasmic kwashiorkor and the one with marasmus have an excess of body water, the presence or absence of oedema may seem immaterial and to be mere clinical hair splitting. However, although in terms of total body water there is little difference between the two conditions, their clinical appearance and prognosis are quite different (Table 1). Gopalan (1968) has therefore suggested that the kwashiorkor state (oedema present) represents failure of adaptation, while marasmus represents successful adaptation.

### Table 1. Pattern of Malnutrition at MRC unit, Kampala, 1966–67, using Wellcome classification

| Weight as % of Harvard median Oedema | Kwashiorkor | Marasmic Kwashiorkor | Marasmus |
|-------------------------------------|-------------|----------------------|----------|
| 72%                                 | >60         | <60                  | <60      |
| Proportion of all admissions        | 17%         | 16%                  | 12%      |
| Mortality rate                      | 17%         | 29%                  | 4%       |

Protein

Figure 2(a) illustrates the principles of nitrogen balance in a child. Apart from very small losses in the faeces and skin, most of the nitrogen leaving the body is in urine so that the absorbed nitrogen minus the urinary loss gives the apparent retention that is used for growth and general maintenance of tissues. When the protein intake is reduced urinary nitrogen falls by two possible mechanisms; either maintenance turnover remains constant and there is a change in the distribution of nitrogen so that a smaller proportion appears in the urine, Fig. 2(b), or the distribution remains constant and there is a reduction in maintenance turnover, Fig. 2(c). Amino-acid turnover studies suggest that maintenance requirements remain constant (Waterlow and Stephen, 1967; Picou and Waterlow, 1968), and there is a reduction in the proportion of
Fig. 2. Possible mechanisms of adaptation to a low protein intake. The upper figure, (a), shows general principles of nitrogen balance, and the two lower figures, (b) and (c), both show the possible mechanisms resulting in a lower urinary nitrogen in response to a decreased protein intake. (Figure adapted and modified from Waterlow, 1968).
nitrogen excreted in the urine due to, or at least associated with, a reduction in the activity of the enzymes of the urea cycle (Schmike, 1962; Waterlow, 1968b). If the protein intake continues to fall, further losses can be avoided by stopping growth; later still, net maintenance requirements of nitrogen can be lowered by a reduction in the basal metabolic rate, and finally, if necessary, further savings can be made by a reduction in body mass, i.e. by wasting. It is a matter of opinion at what point in this sequence adaptation ends and failure begins.

Newborn babies may experience widely different protein intakes during the first few months of life and Fig. 3 shows the cumulative nitrogen balance data on a human baby during the first 4 months of life as he doubles his birth weight. During that time he will consume 100 litres of milk which, if it is human milk, Fig. 3(a), contains 1,200 g of protein. The net maintenance losses account for the bulk of the urinary nitrogen, so even if the protein intake were lower, it is unlikely that the urinary nitrogen could be reduced further unless there was also a reduction in maintenance turnover and basal metabolic rate. If the 100 litres is cow’s milk, the protein intake is trebled, Fig. 3(b). Maintenance turnover remains the same, but there is considerably greater loss of urinary nitrogen so presumably the urea cycle enzymes in children receiving cow’s milk are very active. This, therefore, is an adaptation to different levels of dietary protein, which is clinically very successful. However, although the babies receiving cow’s milk have greater urinary nitrogen, their apparent retention of nitrogen is still greater than in the breast-fed ones; apparently 800 g of protein are being laid down in the new tissue of the bottle-fed child compared to only 400 g in the breast-fed child, i.e. a divergence of body composition is occurring; the bottle-fed baby is becoming chemically more mature, chemically older. It may be that these differences in the calculated body composition reveal only the limitation of the nitrogen balance technique (Wallace, 1959; Foman and Owen, 1962), but, if a true divergence of body composition does occur, it is almost a teleological problem to decide whether it represents adaptation or failure.

**Changes in Individual Metabolic Processes**
The detailed biochemical sequelae of the classical syndromes of protein calorie malnutrition in developing countries have been widely studied, and this work has been well summarised in various reviews (Viteri et al., 1964; Dean, 1965; McCance and Widdowson, 1968; Whitehead and Alleyne, 1972). The intrinsic biochemical changes associated with intrauterine and perinatal malnutrition are, with a few exceptions such as hypoglycaemia (Cornblath and Schwartz, 1966), less well documented.
Fig. 3. Cumulative nitrogen balance during the first four months of life as the baby doubles its birthweight from 3.3 to 6.6 kg, (a) showing data for a baby receiving human milk, and (b) for a baby receiving cow's milk.
**Table 2. Prevalence of sugar Malabsorption in Children with Kwashiorkor**

| Technique                        | Number of children studied for each individual sugar* | Percentage of children tested who gave abnormal results with the following sugars: | Reference                  |
|----------------------------------|------------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------|
|                                  |                                                      | Lactose | Sucrose | Maltose | Glucose | Galactose | Fructose |                                |
| Stool weight and lactic acid     |                                                      |         |         |         |         |           |          | Bowie et al. (1965) (S. Africa)† |
|                                  | 27                                                   | 85      | 85      | 75      | 75      | 75        | 75       | Bowie et al. (1967)             |
|                                  | 20                                                   | 85      | 85      | 75      | 75      | 75        | 75       | Prinsloo et al. (1969) (S. Africa) |
|                                  | 18-20                                                | 6       | 6       | 10      | 6       | 11        | 11       | Wharton et al. (1968) (Uganda)   |
| Quantitative stool sugars        | 71                                                   | 22      | 22      | 15      | 14      | 11        | 7        | Bowie et al. (1965)             |
| Rise in blood sugar              | 5                                                    | 60      | 60      | 77      | 77      | 77        | 77       | Bowie et al. (1967)             |
|                                  | 10-18                                                | 25      | 25      | 25      | 25      | 25        | 25       | Chandra et al. (1968) (India)    |
|                                  | 100                                                  | 80      | 80      | 60      | 60      | 60        | 60       | James (1970) (Jamaica)‡          |
| Jejunal perfusion                | 10                                                   | 80      | 80      | 60      | 60      | 60        | 60       | Bowie et al. (1965)             |
|                                  | 9-11                                                 | 100     | 100     | 67      | 67      | 67        | 67       | Bowie et al. (1967)             |
|                                  | 11                                                   | 73      | 73      | 45      | 45      | 45        | 45       | Stanfield et al. (1965) (Uganda) |
|                                  | 33                                                   | (14)    | (37)    | (38)§   | (38)§   | (38)§     | (38)§    | Bowie et al. (1967)             |
|                                  | 9                                                    | 66      | 66      | 89      | 89      | 89        | 89       | Prinsloo et al. (1969)          |
|                                  |                                                      |         |         |         |         |           |          | James (1971)‡                    |

* Selection of children for study is not clearly documented in many studies.
† Considerable reduction of stool weight in many children when they were given a disaccharide free diet.
‡ Includes 5 children with marasmus.
§ Mean enzyme level expressed as percentage of normal values.
†† 8 marasmic children also studied. Enzyme levels less frequently and less severely depressed but only 2 children had normal levels of all 3 enzymes.
Some measure of the overall effect of malnutrition on the biochemical processes can be gained by a study of oxygen consumption and metabolic rate. Individual processes, however, will be moderated by enzyme activity and hormone secretion.

**Oxygen Consumption**
Malnourished animals have a reduced oxygen consumption that may result in hypothermia (McCance and Mount, 1960); similar observations have been made in malnourished children throughout the world (Lawless and Lawless, 1963; Brenton et al., 1967). Malnourished newborns also have a reduced oxygen consumption during the first five days of life but this lowered metabolic rate can be quickly raised if the babies are given a higher calorie intake (Scopes and Ahmed, 1966; Bhakoo, 1970). Brooke (1972) showed a rise in the temperature of malnourished Jamaican children when they were fed. It seems that a regular supply of calories is a potent stimulus of metabolism and a good insurance against hypothermia. Reduced oxygen consumption in malnourished children eventually results in a low body temperature; in Uganda hypothermia occurred in about half of the children with kwashiorkor and the death rate among these was twice that of the children who managed to remain warm (Brenton et al., 1967). Although a reduced oxygen consumption may be a useful way of conserving scarce calories, if it eventually results in a fall of body temperature nutritional failure has occurred.

**Enzyme Activity**
The enzymes associated with sugar absorption have clear nutritional importance and illustrate some of the problems associated with enzyme interpretation. Table 2 summarises the investigations of sugar intolerance in malnourished children. Lactose is the main offender but intolerance to other sugars, both disaccharide and monosaccharide, does occur. In many, lactose intolerance persists despite nutritional recovery, probably because they had a hereditary variety of alactasia. Even after excluding the hereditary variety, there is some doubt whether these gut enzyme deficiencies are truly nutritional in origin, since most animals respond to a low protein diet by developing raised levels of disaccharidases in their gut (Solimano et al., 1967). My own view on this apparent paradox is that most animal experiments are merely demonstrations of adaptation to the altered diet and that throughout the experiment the integrity of their enterocytes has been maintained. On the other hand, sugar intolerance in malnourished children represents nutritional failure that has occurred secondarily to the mucosal lesion frequently found in kwashiorkor. However, changes in the levels of the enzymes concerned with
intermediary metabolism may also be difficult to interpret. When a low enzyme activity is observed in a particular tissue it may be that there has been an inadequate synthesis of the protein apo-enzyme or of the co-factor, but it could be merely that the metabolic flux down that particular pathway has been reduced, leading to a secondary fall in enzyme activity, i.e. lack of substrate induction. In some instances a reduced enzyme activity in malnourished children may lead to the accumulation of a substrate, e.g. accumulation of phenylalanine and urocanic acid in children with kwashiorkor (Whitehead, 1964). Low enzyme activity associated with accumulation of substrate seems good evidence that a particular metabolic pathway is failing to meet requirements, and perhaps might be regarded as a specific biochemical sign of nutritional failure.

Hormone Secretions
Table 3 shows the plasma hormone levels of children with kwashiorkor. There are raised levels of growth hormone and cortisol, and reduced levels of insulin. Growth hormone is known to inhibit arginine synthetase, the rate-limiting step in the urea cycle (McLean and Gurney, 1963), and this may partly explain the mechanism of the changes in the urea cycle, which occur in response to different protein intakes. Cortisone promotes protein synthesis in the liver while the low insulin levels result in a reduced uptake of amino acids by the muscles so that the net effect of these hormone changes would be for the liver to gain nitrogen at the expense of peripheral tissues such as muscle. On nutritional recovery the cortisol and growth hormone levels return to normal but insulin levels, although rising, remain well below normal. Cook (1967) has shown a diminished ability to handle intravenous glucose up to seven years after an overt episode of kwashiorkor and he has speculated whether this accounts for the high incidence of pancreatic diabetes in tropical countries. Although some hormone changes may seem a reasonable adaptation to

| Plasma mean values | Before treatment | After treatment | Reference |
|--------------------|-----------------|----------------|-----------|
| Fasting Cortisol (μg/ml) | 29 | 13 | Jamaica (Alleyne and Young, 1966) also India. |
| Fasting growth hormone (µIU/ml) | 20 | 5 | S. Africa (Pimstone et al., 1966) also Uganda, Jamaica. |
| Insulin following IV glucose (μg/ml) | 1.5 | 3.0 | Jamaica (James and Coore, 1970) also Nigeria, not always low in Uganda. |

Table 3. Plasma Hormone Changes in Malnutrition in Children with Kwashiorkor
nutritional stress, if the change is permanent despite adequate nutritional repletion, and this change eventually results in secondary disease, it seems that adaptation has been left behind and nutritional failure has begun.

**ENVOI**

Malnutrition in children is associated with numerous changes in the intrinsic metabolic processes, leading eventually to a change in body composition and an altered rate of chemical development. Many of these changes are clinically important and are associated with an adverse prognosis, while others seem commendable adaptation to the environment. Table 4 lists those points that might tentatively be taken as signs that adaptation and compensation have broken down and that the state of nutritional failure exists. Some points belong to the realm of classical pathology, some to modern biochemistry; others rest on careful observation of the natural history of malnutrition. It is these qualities, the need to call on many disciplines and on a wide variety of knowledge, that makes nutrition such an intriguing subject for the paediatrician.

This article is based on a paper read at the College Conference on Metabolic Aspects of Disease held in Cardiff in September 1972.

**Table 4. Evidence of Nutritional Failure**

| 1. Cell damage:     |
|---------------------|
| (a) Histology; e.g. jejunum, myocardium |
| (b) Biochemical; e.g. raised LDH |
| 2. Association with death: |
| (a) Clinical; e.g. oedema, hypothermia |
| (b) Biochemical; e.g. raised hydroxyproline excretion |
| 3. Permanent change despite rehabilitation: |
| (a) Anthropometry |
| (b) Endocrine; e.g. depressed insulin secretion |
| 4. Certain metabolic changes: |
| (a) accumulation of metabolite; e.g. urocanic acid |
| (b) depression of maintenance metabolism |

References

Alleyne, G. A. O. and Young, V. H. (1966) *Lancet*, 1, 911.
Bhakoo, O. H. (1970) *Archives of Disease in Childhood*, 45, 712 (Abstract).
Bowie, M. D., Brinkman, G. L. and Hansen, J. D. (1965) *Journal of Pediatrics*, 66, 1083.
Bowie, M. D., Barbezat, G. O. and Hansen, J. D. L. (1967) *American Journal of Clinical Nutrition*, 20, 89.
Brenton, D. P., Brown, R. E. and Wharton, B. A. (1967) *Lancet*, 1, 410.
Brock, J. F. and Hansen, J. D. L. (1965) *In Human Body Composition*, p. 245. (Ed. J. Brozek). Oxford: Pergamon Press.
Brooke, O. G. (1972) *British Medical Journal*, 1, 331.
Cassady, G. (1970) *Pediatric Clinics of North America*, 17, 79.
Chandra, R. K., Pawa, R. R. and Ghai, O. P. (1968) *British Medical Journal*, 4, 611.
Cook, G. C. (1967) *Nature* (London) **215**, 1295.
Cornblath, M. and Schwartz, R. (1966) *Disorders of Carbohydrate Metabolism in Infancy*. Philadelphia: Saunders.
Crabbé, P. and Isselbacher, K. J. (1965) *Gastroenterology*, **48**, 307.
Dean, R. F. A. (1965) In *Recent Advances in Paediatrics*, 3rd edition, p. 234. (Ed. D. Gairdner). London: Churchill.
Foman, S. J. and Owen, G. M. (1962) *Pediatrics*, **29**, 495.
Garrow, J. S., Smith, R. and Ward, E. E. (1968) *Electrolytic Metabolism in Severe Infantile Malnutrition*, p. 26. Oxford: Pergamon.
Gopalan, C. (1968) In *Protein Deficiencies and Calorie Deficiencies*, p. 49. (Ed. R. A. McCance and E. M. Widdowson). London: Churchill.
James, W. P. T. (1970) *Clinical Science*, **39**, 305.
James, W. P. (1971). *Archives of Disease in Childhood*, **46**, 218.
Lawless, J. and Lawless, M. M. (1963) *Lancet*, **1**, 1082.
McCance, R. A. and Widdowson, E. M. (1968) *Protein Deficiencies and Calorie Deficiencies*. London: Churchill.
Picou, D. and Waterlow, J. C. (1968) In *Amino Acid Metabolism and Genetic Variation*, p. 421. (Ed. W. L. Nyhan). London: McGraw-Hill.
Prinsloo, J. G., Wittman, W., Pretorius, P. J., Kruger, H. and Fellingham, S. A. (1969) *Archives of Disease in Childhood*, **44**, 593.
Schmike, R. T. (1962) *Journal of Biological Chemistry*, **237**, 1921.
Viteri, F., Behar, M., Arroyave, G. and Scrimshaw, N. S. (1964) In *Mammalian Protein Metabolism*, Vol. 2, p. 523. (Ed. H. M. Munro and J. B. Allison). New York: Academic Press.
Waterlow, J. C. and Stephen, J. M. L. (1967) *Clinical Science*, **33**, 489.
Whitehead, R. G. (1964) *Clinical Science*, **26**, 271, 279.
Whitehead, R. G. (1965) *Lancet*, **2**, 567.