

**Oedema in protein energy malnutrition: the role of the sodium pump**

By J. PATRICK,\* *Tropical Metabolism Research Unit, University of the West Indies, Kingston 7, Jamaica*

***Oedema in protein energy malnutrition (PEM)***

For a long while opinion has been divided between those who view marasmus and kwashiorkor as ends of a spectrum and those who view them as distinct entities. I do not wish in this paper to enter into that discussion except in so far as it is necessary to try to understand why the child with kwashiorkor has had an episode of positive sodium balance which the child with marasmus has avoided. In the midst of the discussions about aetiology it is sometimes forgotten that oedema always implies an expansion of total body Na which is mainly in the extracellular fluid. Because there is very little, if any, control of Na absorption from the diet, oedema also implies abnormal renal handling of Na. Unfortunately despite many years of research our understanding of the normal physiology of Na re-absorption by the kidney is still incomplete; in particular the means whereby the kidney restores Na balance after acute expansion of the extracellular space with saline is not understood and it is this mechanism which has failed in kwashiorkor. Without an adequate understanding of the normal physiological response to expansion of the extracellular volume it is impossible to give a detailed mechanistic account of oedema. We must be content with defining the role of those potential explanations which have some current support and discussing the possible mechanisms which have not yet been thoroughly investigated. My task is to discuss the role of the Na pump but as I hope to make clear the Na pump cannot be discussed meaningfully without parallel consideration of membrane permeability to Na and potassium.

A general review of nutritional oedema has recently been published and this provides an excellent introduction to the literature (Alleyne *et al.* 1977).

Undoubtedly most physicians and nutritionists caring for malnourished children have been impressed by the fall in serum albumin which is so characteristic of kwashiorkor. Nevertheless correlation does not prove causality. One can argue that some extent of correlation between reduction in serum albumin and extent of oedema is almost inevitable. The argument goes as follows. James & Hay (1968) showed that the synthesis rate of albumin was low in malnutrition and that it seemed to depend upon the dietary intake of protein. Thus if a child with malnutrition develops Na retention for whatever cause the serum albumin level must fall with the development of oedema and increase with its loss.

If the relationship between serum albumin and oedema is causal then a low serum albumin ought to be always associated with nutritional oedema and nutritional oedema ought not to occur in the absence of hypoalbuminaemia.

\*Present address: Medical Unit, St Thomas' Hospital, London SE1.

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The results presented by Montgomery (1963) bear on this point; the results show clearly that low albumin values can occur in children without oedema (less than 1% of weight loss after admission to hospital). Furthermore many children have oedema with serum albumin values above 20 g/l which is the level at which acute reductions in albumin usually induce oedema. Two weight charts illustrating these points are shown in Figs. 1 and 2. These children were given only 0.6 g protein and 0.38–0.42 MJ (90–100 kcals)/kg per 24 h together with K and magnesium supplements and in the second instance 50 ml fresh blood. The diuresis in both cases was striking and amounted to approximately 20% of body-weight. If all the excess fluid was originally in the extracellular fluid (ECF) then the ECF had halved, assuming the final ECF space to be normal. With such large changes it is difficult, though not impossible, to explain the results on the basis of redistribution

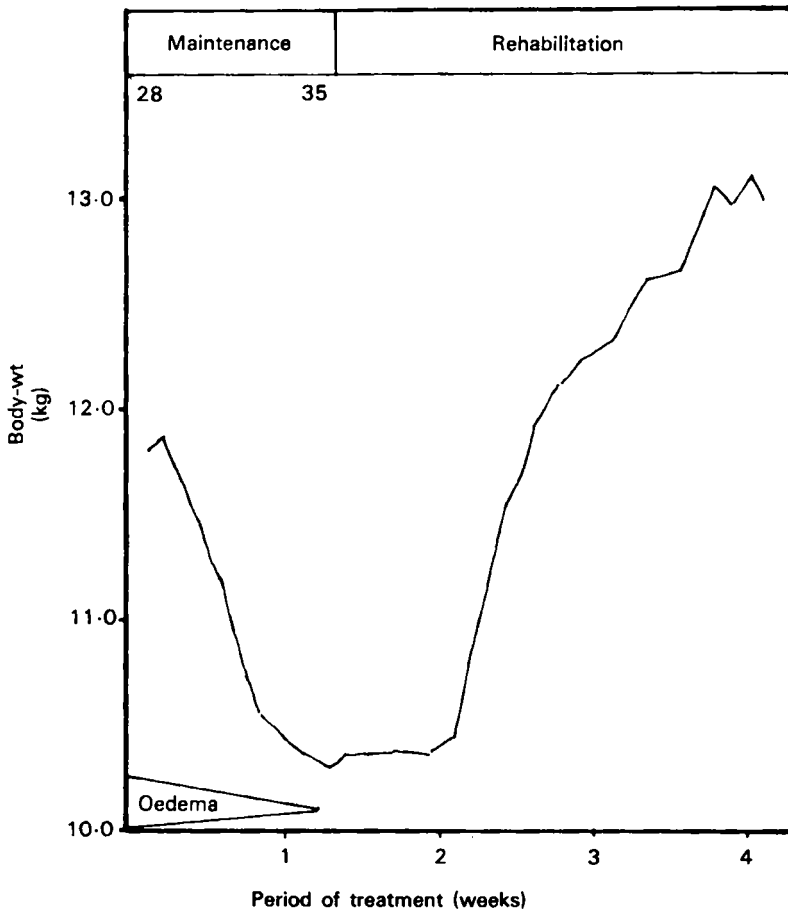


Fig. 1. This patient, aged 27 months, lost almost 20% of his oedema free weight in the first 10 d after admission. The lowest serum albumin on admission was 28 g/l which had increased to 35 g/l after loss of oedema. During this period he received 0.6 g protein and 0.38–0.42 MJ (90–100 kcals)/kg per 24 h together with potassium and magnesium supplements. This weight loss, if all from the extracellular fluid, would represent a reduction of more than 50%, assuming a normal value at the end of 10 d.

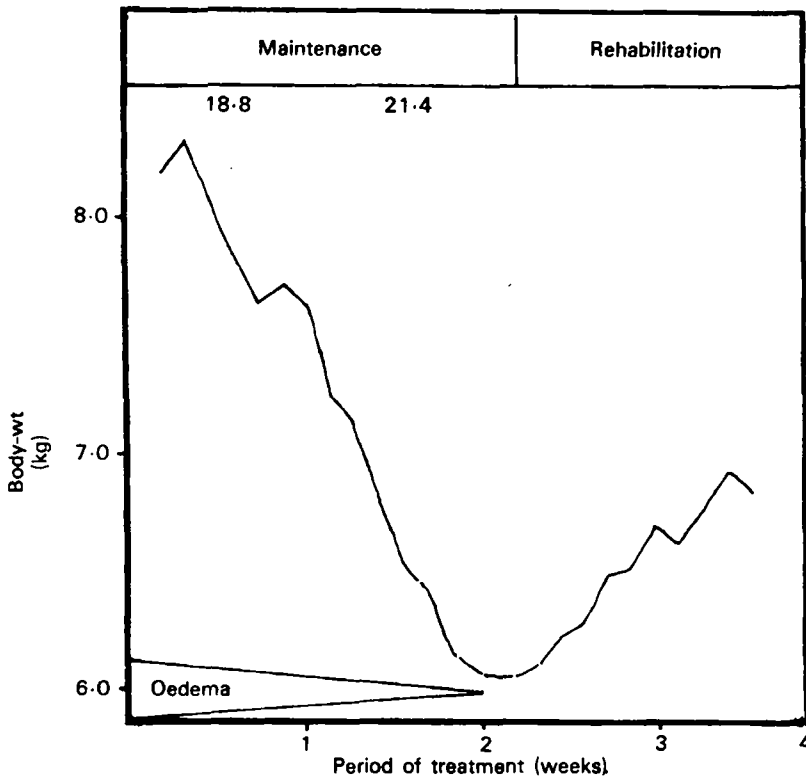


Fig. 2. In contrast to patient no. 1 (Fig. 1) this child aged 14 months had an initial serum albumin of 18.8 g/l which increased to 21.4 g/l in 2 weeks. During this time she lost over 2 kg of weight. Assuming a normal extracellular fluid space at the end of 2 weeks this would be equivalent to a reduction of 60%.

of albumin with consequent alterations in fluid distribution dependent upon the osmotic effects of albumin.

The osmotic importance of albumin is undeniable but that other compensatory mechanisms can also control ECF volume seems to me equally undeniable. This view is further emphasized by the rare but important syndrome of *analbuminaemia* in which children are born without any serum albumin and yet they do not develop severe oedema (Bennhold *et al.* 1954). The fascinating experimental work of Levy (1977) is also pertinent to this argument. He has studied meticulously the relationships between Na retention, albumin and plasma volume in experimental cirrhosis in dogs. He made several interesting observations of which the most relevant to this discussion was the finding that Na retention began before serum albumin fell and before plasma volume expanded.

Over the last few years in Jamaica the length of time that newly-admitted children are studied before attempting to rebuild their wasted bodies has been gradually extended. We have also attempted to make a metabolic distinction between children who are in a steady-state with respect to lean body mass and those who are gaining weight. To do this we have tried as far as possible to substitute for progressive increments in protein and energy intake a period of

maintenance intake and a rehabilitation period so that the distinction between the two is less blurred than with the traditional graduated feeds. On admission we concentrate on correction of electrolyte deficits, treatment of small bowel overgrowth of bacteria and provision of maintenance amounts of energy and protein. The children are therefore given a diet which only contains 0.6 g protein/kg body-weight per 24 h and 0.40–0.42 MJ (95–100 kcal)/kg body-weight per 24 h. These values are derived from the work of Chan & Waterlow (1966) and Kerr *et al.* (1973) and represent the lowest dietary protein level at which nitrogen balance can be maintained and the zero weight gain intercept for the regression of energy intake on weight gain derived from a large series of recovering malnourished children. This initial period of low protein intake also limited the rate of resynthesis of albumin so that on occasion we have been surprised to see the situation in which the natriuretic response of the kidney returned before serum albumin had been restored.

It is reasonable to ask how these results fit in with the classical studies which showed that acute reductions in serum albumin in animals induced Na retention and oedema. I do not know the answer but apart from the explanations so convincingly described by Dr Coward in this symposium (Coward & Fiorotto, 1979), it is worth pointing out that acute removal of serum proteins is associated with acute removal of many other substances such as trace metals which may be important in the maintenance of membrane permeability, a subject which I hope to show is very pertinent to our understanding of oedema.

Before discussing Na transport at a cellular level a brief comment about renal function in PEM is necessary. Moderate reductions in glomerular filtration rate (GFR) and renal blood flow have been documented in PEM and these will undoubtedly aggravate the tendency to salt retention as will the increased levels of salt-retaining hormones (see Alleyne *et al.* 1977). However, the normal kidney can excrete salt and water in response to expansion of the ECF despite a low GFR and the presence of maximal amounts of salt-retaining hormone. Clearly in severe PEM it is this mechanism which is grossly impaired (for review of renal function in PEM, see Klahr & Alleyne, 1973). Thus we can conclude that either the signals from the 'volume receptors' are inhibited or the kidney cannot regulate the rate of Na re-absorption from the nephron in response to ECF expansion because of an intrinsic defect.

Such an intrinsic defect could arise because the luminal surfaces of the renal tubular cells had changed their permeability to Na, as well as for the more frequently cited reasons of changes in post-glomerular oncotic pressure, or in the secretion of a natriuretic hormone. The arguments about the effect of changes in serum albumin concentration on renal tubular Na re-absorption are by no means settled with different workers reporting opposite results. Similarly the search for a natriuretic hormone has also gone through a series of false alarms. There is not space to discuss these aspects in this paper but they are both the subject of frequent review (for references, see DeWardener, 1977).

I wish instead to discuss the possibility that a change in membrane permeability

or in the Na pump could be the underlying mechanism. The most widely accepted model of membrane structure is that of Singer & Nicholson (1972) which consists of the classical lipid bilayer with proteins showing lateral mobility set into it. These proteins include the Na pump and probably the 'channels' whereby Na and K move down their respective electrochemical gradients. The function of the pump and the permeability of the membrane can be modified in a variety of ways, for example by altering the phospholipid:cholesterol ratio or by altering the nature and type of fatty acids in the membrane (Claret *et al.* 1978). The pump also appears to be extremely sensitive to small amounts of vanadate (Beaugé & Glynn, 1978) whilst permeability is very dependent upon other trace metals (Castranova & Miles, 1976; Patrick *et al.* 1978).

In the renal tubular cell it is currently thought that Na moves from the lumen to the cell down its electrochemical gradient. It is then pumped out of the cell on the capillary side in exchange for K. Thus net transport of Na across the tubular cell is achieved.

In isolated cells like erythrocytes and white blood cells no net transport occurs but active transport balances the downhill movements of Na and K to achieve a steady-state. Normally, the stoichiometry of the pump is thought to be fixed with 1 mol ATP expended for 3 mol Na pumped out and 2 mol K pumped in. Incidentally many nutritionists seem unaware of the implication of this statement namely that somewhere between 30–40% of our basal energy expenditure is accounted for by this mechanism. However, other modes of function can also occur but they are not quantitatively important under physiological circumstances (Edelman, 1974, 1976). The other important feature of this system is that alterations in the setting of the pump only make transitory changes in the rate of Na transport unless there is also a change in the rate of downhill movement. This is perhaps more important in an epithelial tissue such as the renal tubule, where re-absorption of Na filtered by the glomerulus depends upon Na transport by the tubular cells. In this instance the Na pumps are situated on the capillary side of the cell and thus do not pump Na across the luminal membrane but work at a rate sufficient to maintain intracellular Na constant. This rate is therefore determined by the movement of Na down its electrochemical gradient into the cell. In other words it is dependent upon the permeability of the membrane to Na. It is possibly at this point that the control of Na balance following saline infusion is achieved. Alternatively the excretion of a saline load could be achieved by inhibition of the maximal rates of Na transport and an increase in tubular cell Na content. Vanadate may do this.

There is some circumstantial evidence that Na transport is disturbed in severe malnutrition. The acute effects of impairment of the Na pump are to reduce intracellular K and increase intracellular Na. Studies of body composition in severe malnutrition have shown a consistent trend in this direction. It can be argued that partial inhibition of the Na pump does not necessarily lead to a reduction in cellular K unless there is also a change in membrane permeability to K. Although we would ideally like to understand renal handling of Na and K at a cellular level, the only cells which are easily available are erythrocytes and leucocytes. These cells

are admittedly a long way from renal tubular cells but they do possess Na pumps. I have chosen to use leucocytes for the reasons that they are more like most other cells than erythrocytes in that they have a nucleus, mitochondria and both aerobic and anaerobic pathways for energy production. Polymorphs also have a short life-span and thus theoretically may be more sensitive to short-term changes in diet. In order to look at these systems in cells derived from malnourished children leucocytes were isolated from whole blood and the rates of uptake or loss of  $^{22}\text{Na}$  were measured together with measurement of intracellular Na and K. The methods have been described in detail (Hilton & Patrick, 1973; Patrick & Hilton, 1973). Table 1 shows the values for leucocyte K, Na, the rate-constant for Na efflux and the efflux rate subdivided into glycoside-sensitive and -insensitive components. These results illustrate the changes measured between samples obtained as near to admission as possible and after definite evidence of resolution of oedema had appeared.

Table 1. *Leucocyte electrolyte and sodium transport measurements in kwashiorkor*

(Measurements were made as near to admission as possible and after definite evidence of loss of oedema both clinically and as weight loss had been observed. During the whole period of the study the children received a standard diet which gave 0.6 g protein and 0.40–0.42 MJ (95–100 kcal)/kg body-weight per 24 h. All results are given as mean values with their standard errors)

Measurements	With oedema			Without oedema			
	Mean	SE	n†	Mean	SE	n	
Intracellular Na (mmol/kg dry solids)	182	15	16	119	1.5	13	**
Intracellular Na (/mmol cell water)	74.0	5.4	16	55.3	6.8	13	*
Intracellular K (mmol/kg dry solids)	358	12	17	335	16	13	NS
Intracellular K (/mmol cell water)	143	6	17	156	8	13	NS
Rate-constant for total Na efflux (/h)	4.02	0.25	15	4.06	0.17	10	NS
Ouabain-sensitive rate-constant (/h)	2.88	0.23	6	2.33	0.22	6	NS
Ouabain-insensitive rate-constant (/h)	0.46	0.08	6	1.72	0.14	6	**
Total Na efflux (mmol/kg dry solids per h)	731	89	15	514	59	10	NS
Ouabain-sensitive Na efflux (mmol/kg dry solids per h)	484	50	6	314	52	6	*
Ouabain-insensitive Na efflux (mmol/kg dry solids per h)	78	14	6	259	46	6	**

NS, not significant.

\* $P < 0.05$ , \*\* $P < 0.01$ .

†Because of limitations on samples available from these children ouabain studies were only possible in a small proportion of the total number of studies and hence ouabain-sensitive and insensitive fluxes do not exactly match the total fluxes.

The most interesting result is that for the transport rate of Na which is dramatically increased in kwashiorkor. This can only be achieved by a primary increase in the permeability of the membrane to Na with subsequent stimulation of the Na pump and if the same phenomenon occurred elsewhere, as for instance in the renal tubule, it would be expected to lead to an increased fractional re-absorption of Na and hence Na retention and oedema. Recently Kaplay (1978) has

published results obtained from erythrocytes showing an increase in the NaK ATPase in kwashiorkor which fits in well with these results because for the cell to maintain a steady-state the increased permeability must be balanced by increased pumping.

The next phase of investigation must be an attempt to find out what is responsible for the alteration in permeability. The list of measures which will alter membrane permeability is quite extensive. Individual molecules like valinomycin and gramicidin can do it acutely, trace metals such as zinc, copper, cobalt and nickel can also increase permeability in dog erythrocytes (Castranova & Miles, 1976). We have shown a similar effect in human leucocytes for zinc (Patrick *et al.* 1978). It has also been suggested that catechol amines can do it in brown fat and that this is the mechanism of thermogenesis (Girardier *et al.* 1968; Horowitz, 1973). Alterations in the ratio cholesterol:phospholipid have also been shown to alter membrane fluidity and permeability and it seems likely that the proportions of saturated to unsaturated fatty acids in the membrane will also be important (Chapman & Quinn, 1976). Recently it has been demonstrated that the cholesterol content of the erythrocyte membrane can have quite complex effects on the Na pump depending upon the concentration of intracellular sodium (Claret *et al.* 1978). Thus it seems we are approaching a state where the interactions between alterations in membrane lipids, which may be produced by dietary means, and modification of Na transport will be more precisely understood. Maybe the day is not too far distant when nutritionists will be able to manipulate diet to alter membrane transport in a precise way and thereby correct nutritional oedema quite specifically.

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