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Homeostatic Mechanisms in the Utilization of Exogenous Iron in Children Recovering from Severe Malnutrition

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Summary: We evaluated the role of initial iron stores on iron accumulation during recovery from severe edematous protein–energy malnutrition in children. Twenty-six preschool children were divided in two groups according to their initial iron reserves, as estimated from serum ferritin concentration, using a cutoff criterion of 30 ng/ml. The low ferritin (LF) group had a mean serum ferritin level of 12 ± 8 ng/dl, and the high ferritin (HF) group, 86 ± 32 ng/dl. Both groups had similar degrees of malnutrition and of anemia, as defined by hemoglobin concentration. All children received an adequate therapeutic diet and 60 mg iron daily as ferrous sulfate. The recovery of biochemical and anthropometric indicators of nutritional status, as well as of hemoglobin concentration, was similar in both groups. On the contrary, the LF group showed a marked increase in serum ferritin concentration from the onset of treatment, whereas the HF group had a net decline in this parameter by 30 days, and a stable level thereafter. The difference in serum ferritin concentration between groups was maintained until day 60, and both groups ended the study (90 days) with similar levels. Estimation of the utilization of exogenous iron from changes in total-body iron during the first 60 days of recovery showed the LF group to retain an average of 9.3% of iron intake, whereas the HF group retained only 1.4%. These results confirm that similar degrees of anemia in severe malnutrition can be associated with markedly different iron reserves, and suggest that the homeostatic regulation of intestinal iron absorption by the storage iron pool may produce a lower utilization of oral iron supplements in malnourished children with high iron reserves at the onset of treatment. Key Words: Exogenous iron—Anemia—Protein–energy malnutrition—Serum ferritin—Total iron-binding capacity.

Since low levels of circulating hemoglobin (Hb) are frequently found in children with protein–energy malnutrition (PEM), there has been enduring interest in the study of iron metabolism in malnourished children. Undoubtedly, iron deficiency is a frequent feature of PEM, and can by itself account for the low Hb production. On the other hand, it has been pointed out that the anemia of kwashiorkor is also an adaptative phenomenon: the red cell mass is determined by the oxygen demands of actively metabolizing tissues, and since lean body mass is reduced in severe malnutrition, a compensatory reduction in oxygen transport capacity (circulating Hb) is appropriate, to spare amino acids for other synthetic functions (1).

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A variable incidence of iron malabsorption has also been reported in PEM (2,3), but its cause is not fully understood. Since a host of derangements in gastrointestinal function has been documented in PEM (4,5), it can be speculated that iron malabsorption results from nutritional damage to the intestinal mucosa. Another interpretation could be related to the homeostatic regulation of intestinal iron absorption by iron stores, a fact well established for experimental animals (6–8) and for normal men (9,10), but little explored in the severely malnourished child.

The development of the radioimmunoassay determination of serum ferritin (SF) provided a convenient, noninvasive method for the assessment of iron reserves (11,12), and equations for estimating storage and total-body iron from SF values have been proposed (13). In the present study we have used the sequential changes in SF concentration to

assess the repletion of iron stores in severely malnourished children during the first 90 days of nutritional rehabilitation, while they received therapeutic supplements of ferrous sulfate. The results suggest that the size of the storage iron pool at the onset of treatment may have an important influence in the ability of the malnourished child to utilize oral iron supplements during the nutritional recovery.

PATIENTS AND METHODS

The patients were preschool children of Mayan or ladino descent, aged 18–40 months, admitted to the Clinical Research Center of the Institute of Nutrition of Central America and Panama (INCAP) with diagnosis of severe edematous PEM (kwashiorkor or marasmic kwashiorkor). This diagnosis was based on past clinical history, physical examination, low plasma protein concentration, and deficit of weight-for-height. The series consisted of 26 children from 32 consecutive admissions to the unit. Six children with protracted infections or who were unable to receive the standard therapeutic diet owing to vomiting or other complications were excluded from the study. The protocol was approved by the Human Studies Committee at INCAP. The parents of all children studied gave written consent after the purpose and procedures of the study were clearly explained. The children were treated according to the standard therapeutic program used in INCAP (13), which included a gradual increase in dietary protein and energy until 4 g/kg/day milk protein and 150 kcal/kg/day were reached by the 8th day of hospitalization. This intake was maintained until each child had recovered completely; a mixed diet was then offered *ad libitum* until discharge. Vitamin and mineral supplements were included as part of the therapeutic regimen (13). Starting 2–3 days after admission, 60 mg elemental iron was administered every morning before breakfast (as 300 mg ferrous sulfate).

The nutritional recovery of the children was monitored daily by measurement of body weight and weekly by complete anthropometry. These procedures, as well as the preparation and assessment of dietary intake, have been described in detail elsewhere (14).

Hematological and Biochemical Determinations

On admission and at intervals of ~30 days, determinations were made of microhematocrit, Hb concentration, serum iron, total iron-binding capacity (TIBC), and percent saturation of transferrin (15). SF was determined by the immunoradiometric assay (Fer-Iron kit, Ramco Laboratories Inc., Houston, TX) (16,17). Total plasma protein concentration was also determined. Urinary creatinine excretion was measured at monthly intervals in 72-h urine collections (18), and the creatinine–height index was calculated as an indicator of lean body mass (19).

RESULTS

Classification into Groups with High or Low Iron Stores on Admission

Based on the distribution of SF concentration on admission, the 26 children were divided into groups with higher ferritin (HF) and lower ferritin (LF) concentration, with a cutoff criterion of 30 ng/ml—a level reported to be the median (20) and close to the mean (21) SF concentration in normal children of this age. The groups formed using this criterion had significantly different mean SF concentrations ($p < 0.001$). The HF group also had higher serum iron concentration, TIBC, and percent saturation of transferrin than the LF group. The anthropometric and biochemical indicators of nutritional status on admission were similar in both groups, as were the hematocrit and Hb concentration (Table 1).

Clinical and Nutritional Outcome

All children in both groups had an adequate nutritional recovery. Their average weight-for-height after 90 days of treatment was 99 ± 5% in the LF group and 95 ± 8% in the HF group; the corresponding creatinine–height indices were 0.93 ± 0.08 and 0.95 ± 0.02, respectively. Several children from both groups had mild episodes of upper respiratory tract or localized skin infections, but children with febrile syndrome or anorexia were excluded from the study. Seven children (4 in the HF and 3 in the LF group) received systemic antibiotics for 5–7 days.

Hematological Changes During Recovery

On admission, the mean Hb concentration of our patients was 2.2 g/dl below the normal values for

TABLE 1. *Nutritional and hematological data on admission in the children studied*

	Status of iron reserves	
	Low	High
Nutritional status		
Age (months)	22 ± 5	24 ± 6
Weight (kg)	7.2 ± 1.0	6.9 ± 1.2
Height (cm)	75.1 ± 3.8	75.0 ± 4.2
Weight-for-height (%)[a]	75 ± 9	71 ± 7
Creatinine–height index	0.63 ± 0.13	0.65 ± 0.16
Hematological data		
Hematocrit (%)	31 ± 4	29 ± 3
Hemoglobin (g/dl)	9.8 ± 1.8	9.3 ± 1.1
Serum iron (μg/dl)	39.5 ± 20.8[b]	62.6 ± 18.2[b]
TIBC (μg/dl)	196 ± 108[b]	115 ± 32[b]
Saturation of transferrin (%)	28 ± 21[b]	57 ± 19[b]
Serum ferritin (ng/ml)	12 ± 7[c]	86 ± 32[c]

Values are means ± SD. TIBC, total iron-binding capacity.
[a] Percent of adequacy in reference to 50th percentile, National Center for Health Statistics tables.
[b,c] Group differences (Student's *t* test): $p < 0.05$ and $p < 0.001$, respectively.

Guatemalan children of the same age (22), and was representative of previous findings in PEM children reported from INCAP (1,23) and from other developing countries (24–27). The serial changes in Hb, serum iron, and TIBC throughout the study are shown in Fig. 1. The mean Hb concentrations were similar in HF and LF groups at all stages of recovery (Fig. 1A). By 90 days, mean Hb values were 11.7 and 11.6 g/dl in the LF and HF group, respectively. The initial difference in serum iron concentration (Table 1) decreased slightly at day 30, to 42.1 ± 22.5 (LF group) and 60.5 ± 26.4 μg/dl (HF group), and disappeared at day 60 (Fig. 1B). At day 30, both groups showed a marked increase in TIBC values, reaching comparable levels (Fig. 1C). At the same time interval, the saturation indices fell to 12 ± 8 and 17 ± 6% in the LF and HF groups, respectively. At the end of the study, percent saturation was 25 ± 11% in the LF group and 19 ± 5% in the HF group.

The changes in SF concentration are shown in Fig. 2. The initial difference in this parameter between the two groups was still statistically significant at day 30. However, by day 60 of treatment the groups showed similar SF values.

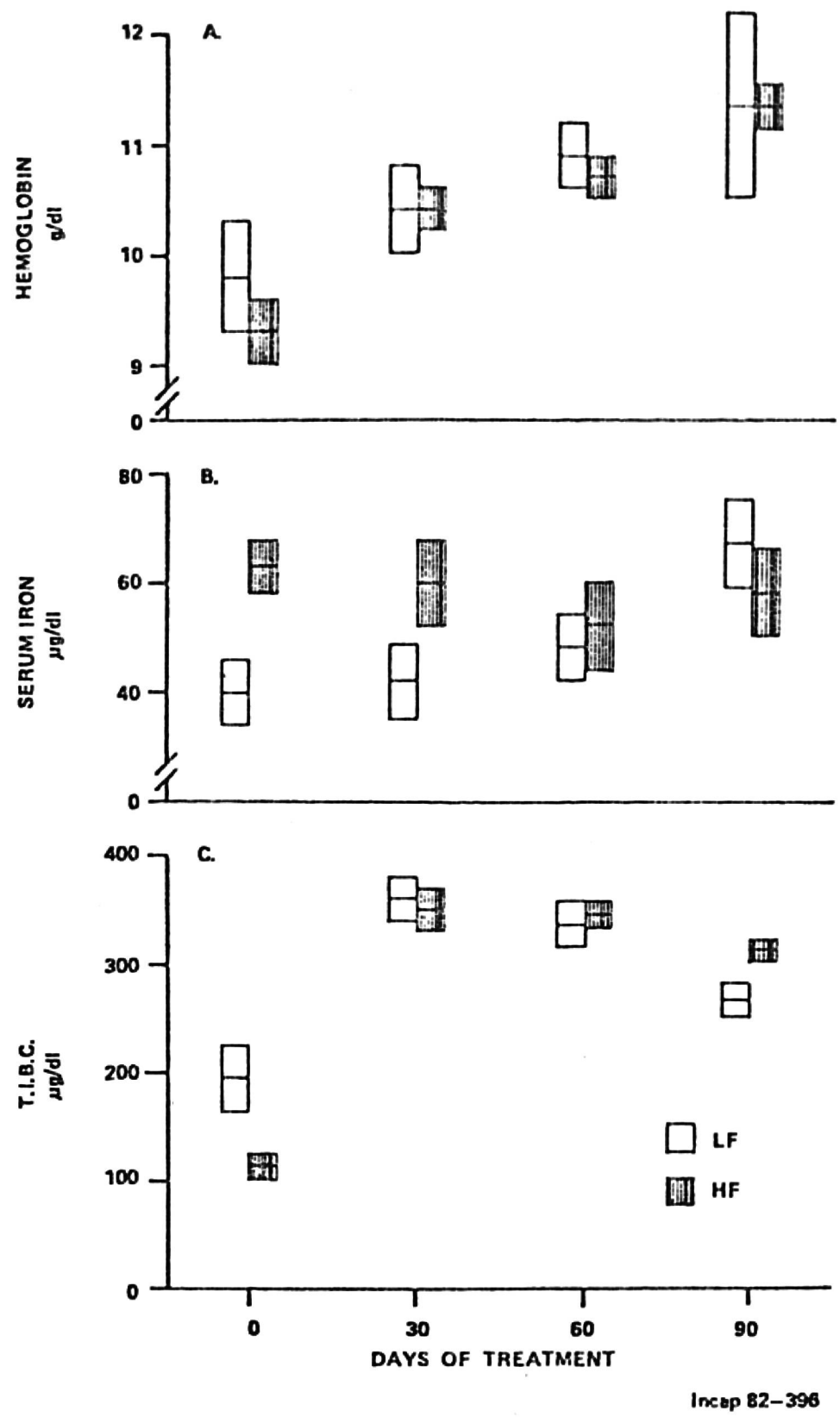

FIG. 1. Serial changes in hemoglobin, serum iron, and total iron-binding capacity (TIBC) in children with low (LF; n = 13) or high (HF; n = 13) serum ferritin on admission. Values are means ± SD. Differences between groups in mean serum iron and TIBC at day 0 are significant ($p < 0.05$).

DISCUSSION

The absence of an efficient physiological mechanism by which the organism can eliminate excess iron requires a strict regulation of its uptake at the intestinal level, to avoid undesirable iron accumulation in the body. In healthy individuals this regulation is homeostatically related to the size of the storage iron pool (9,10). On the other hand, in a significant proportion of children with PEM, a low Hb level coexists with normal or even high iron reserves (2,28,29). We therefore reasoned that, if the homeostatic regulation of intestinal iron absorption was operative in PEM, those children would show a lower intestinal avidity for ingested iron. The results of the present study confirm this possibility.

The hematological profiles of the groups studied differed in three classical indicators of iron status:

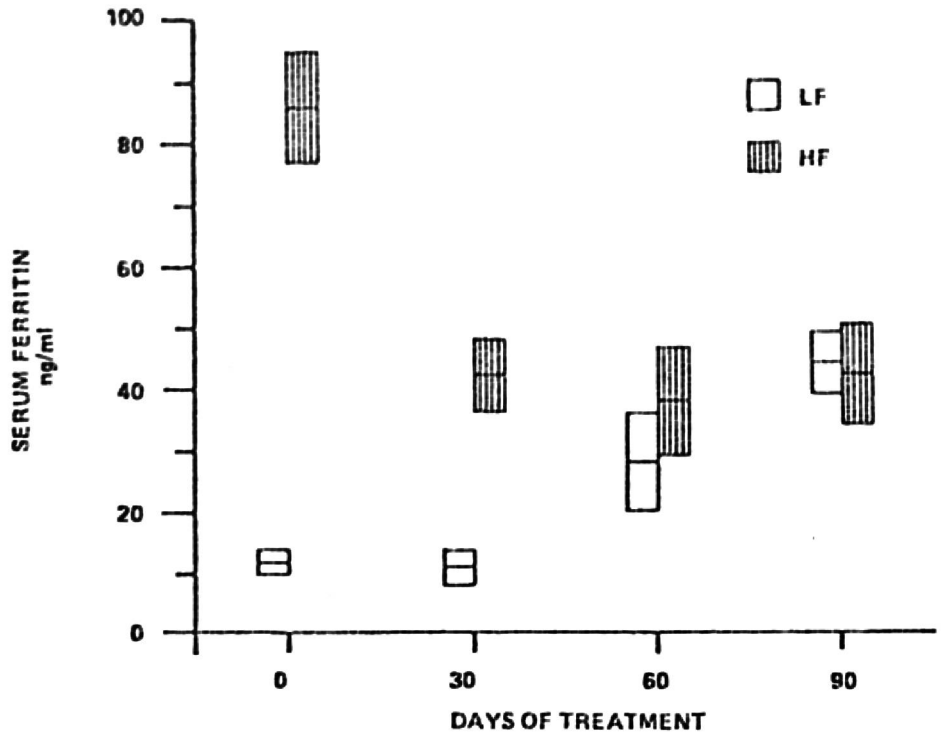

FIG. 2. Changes in serum ferritin concentration during the study in children with low (LF; n = 13) or high (HF; n = 13) serum ferritin on admission. Values are means ± SD. Differences between groups are significant at day 0 ($p < 0.001$) and at day 30 ($p < 0.05$).

serum iron, TIBC, and SF (Table 1). The higher serum iron and lower TIBC in the HF group were consistent with a normal iron status, as suggested by the SF values. Thus, it can be proposed that, in this group, the low Hb concentration was mainly dependent on an adaptative adjustment to the decreased lean body mass. On the other hand, in the LF group a similar Hb level was associated with markedly low SF values, suggesting that this low Hb concentration was the combined result of the adaptative hemopoietic response and of iron depletion.

The early reports on the anemia of kwashiorkor stressed the inability of the malnourished child to utilize oral iron supplements and even suggested the routine use of the parenteral route for the treatment of iron deficiency (30,31). In a study by Lynch et al. (2), iron absorption in malnourished children was measured by a tracer technique using ^{59}Fe. At the same time, stainable iron was determined in bone marrow biopsy specimens. In the 12 studies performed in children having 0 or 1+ levels of stainable iron in bone marrow, the mean fractional absorption of tracer iron was 35 ± 26%, whereas in the six children with iron reserves rated as 2+ or 3+, fractional absorption was 10 ± 7%. As no supplemental iron was given during recovery, many children depleted their initial iron stores during nutritional recovery. This depletion was associated with an increased fractional absorption of iron in follow-up studies some 30 -60 days after admission. These findings suggest that the regulatory control of intestinal iron absorption by iron reserves is present even in severely malnourished children. Our results, using SF concentration as an indicator of iron reserves, are also consistent with this conclusion.

The issue of iron malabsorption in malnourished children was raised again more recently by Massa et al. (3). These investigators studied the rise in plasma iron after an oral dose of 3 mg/kg ferrous sulfate in a group of children with marasmic or marasmic kwashiorkor malnutrition. Seven of the 25 children had a low plasma iron response, which reverted after about 90 days of nutritional treatment with high-protein, high-energy diets. However, these children actually increased their red cell mass during the study at the same pace as other children with higher ferremic response, even when they received only 15 mg iron/day. Therefore, either the ferremic response is not an adequate indicator of the ability to absorb iron, or these children utilized their iron reserves to produce Hb, or both. Moreover, since the status of iron stores was not assessed, differences in iron absorption could simply reflect that the population studied was heterogeneous in terms of iron status.

An excellent correlation between SF concentration and bone marrow iron has been reported in normal subjects and in patients with iron deficiency or overload (32–34), and equivalencies of 8–12 mg stored iron/ng/ml circulating ferritin have been proposed (33,34); however, these figures have not been validated in malnourished children. Nevertheless, if we use these reported equivalencies for a limited factorial estimation of iron retention (35), the mean daily retention during the first 60 days of treatment would be 9.3% for the HF group and 1.4% for the LF group.

The possible pitfalls in the interpretation of SF values in malnourished children should also be addressed. This protein is a component of the "acute phase" group of circulating macromolecules, and, as such, is known to increase in response to infection, inflammatory processes, and certain types of neoplasias (36,37). Although we excluded patients with severe infections or febrile syndrome, it could be argued that the HF group simply reflected those children with covert infectious processes. One argument against this possibility is that the difference between the HF and LF groups was not restricted to ferritin, but included serum iron and TIBC, the classic indicators of iron status. Moreover, while

during infectious processes the rise in SF is associated with a marked fall in serum iron, the HF group showed the opposite. Also, the time course of SF changes described during infectious processes is at variance with our findings in the HF group. In adult volunteers infected with bacterial endotoxin or ethiocholanolone, the maximum increase in SF appeared after 2 days, and returned to baseline values by day 7. The most sustained increase lasted 10 days (38). In another study (39), the serial determination of SF during episodes of infection in renal transplant patients also showed that peak SF values were always reached within a week of the onset, and had a half-life of only 1.5 days. As expected, in both studies the rise in SF was invariably associated with a fall in serum iron concentration (38,39). In our study, the differences in SF levels between the HF and LF groups were maintained until day 60 of treatment. It is highly unlikely that a covert infectious process would affect simultaneously all children of the HF group for such a long period of time, remain undetected, and yet allow for nutritional recovery identical to that of the "uninfected" LF group.

The possibility that protein deficiency *per se* may have an effect on ferritin production should also be considered. To evaluate this possibility, we compared the sequential changes in total plasma proteins with those of SF or plasma transferrin—estimated from TIBC (40)—and found no correlation (data not shown). This result suggests that protein ligands of iron vary independently of other plasma proteins during nutritional recovery, probably responding specifically to iron status and iron intake. Experiments by Drysdale et al. (41) appear to confirm this possibility. They studied ferritin synthesis in liver slices from protein-depleted rats and showed that the ability to increase the synthesis of the ligand in response to iron administration was largely maintained.

The SF levels in the HF group showed a marked fall between admission and day 30. We have previously demonstrated that the marked shifts in water compartments during the early phase of recovery do not produce significant changes in SF concentration (42). On the other hand, it is unlikely that the fall in SF could be explained only by an increased mobilization of storage iron for Hb synthesis. It is possible that, as has been suggested for adults, there is a "leakage" of ferritin from the tissues to the circulation when iron deposits are saturated. Jacobs et al. (43) compared the decrease in SF with the actual loss of iron from serial phlebotomies in human volunteers, and showed that the amount of iron lost per unit decrease in SF concentration was much lower at high SF levels. In any case, the difference between our two groups was maintained even with the lower SF value of day 30.

The reduced lean body mass of the severely malnourished child requires less oxygen transport capacity, and PEM is usually associated with a contraction of the circulating red cell mass (1) and with a decrease in erythropoietin production (44). These adaptative phenomena can be observed associated with either low or normal iron reserves, depending on the previous history of iron intake and on the rate of depletion of body protein. When successful nutritional therapy takes place, the opposite events occur (i.e., an increase in lean body mass with the consequent increased demand of oxygen carrying capacity). The high rate of hemoglobin synthesis at this point can be supported either by an adequate exogenous iron supply or by normal or high iron reserves at the onset of treatment. This fact may explain the contradictory hematological response of PEM children to iron-free, high-protein diets: some PEM children become rapidly anemic during nutritional recovery if they are not provided with therapeutic doses of iron (29), whereas others show a dramatic increase in Hb production in response to protein alone (45), and increases of >2 g of Hb have been reported after 40 days of an iron-free recovery diet (46). It is reasonable to suggest that this different response may be due to differences in iron reserves at the onset of the nutritional therapy. In the present study, all children had an equivalent recovery of hemoglobin concentration, although the individual capacity to retain exogenous oral iron was clearly dependent on the size of the iron reserves on admission. A key physiopathological conclusion is that the homeostatic regulatory mechanism for iron absorption appears to be conserved in most severely malnourished children. Thus, the response to therapeutic oral iron administration in the PEM patient should be evaluated not only based on his/her depletion of the red cell mass, but also accounting for the regulatory effect of the storage iron pool.

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REFERENCES

1. Viteri FE, Alvarado J, Luthringer DG, Wood RP. Hematological changes in protein-energy malnutrition. *Vitam Horm* 1968;26:573–615.
2. Lynch SR, Becker D, Seftel H, Bothwell TH, Stevens K, Metz J. Iron absorption in kwashiorkor. *Am J Clin Nutr* 1970;23:792–9.
3. Massa E, MacLean WC Jr, Lopez Romana G, Martinez Y, Graham GG. Oral iron absorption in infantile protein-energy malnutrition. *J Pediatr* 1978;93:1045–9.
4. Viteri FE, Schneider RE. Gastrointestinal alterations in protein-calorie malnutrition. *Med Clin North Am* 1974;58:1487–505.
5. Suskind R. Gastrointestinal changes in the malnourished child. *Pediatr Clin North Am* 1975;22:873–82.
6. Greenberg NJ, Balcerzak SP, Ackerman GA. Iron uptake of isolated intestinal brush borders: changes induced by alterations in iron stores. *J Lab Clin Med* 1969;73:711–21.
7. Kimber CL, Mukherjee T, Deller DJ. *In vitro* iron attachment to the intestinal brush border and other environmental factors. *Am J Dig Dis* 1973;18:781–91.
8. Linder MC, Dunn V, Isaac F, et al. Ferritin and intestinal iron absorption: pancreatic enzymes and free iron. *Am J Physiol* 1975;228:196–204.
9. Linder MC, Munro HN. The mechanism of iron absorption and its regulation. *Fed Proc* 1977;36:2017–23.
10. Bothwell TH, Charlton RW, Cook JD, Finch CA. *Iron metabolism in man*. Oxford: Blackwell, 1979:7–14.
11. Walters GO, Miller F, Worwood M. Serum ferritin concentration and iron stores in normal subjects. *J Clin Pathol* 1973;26:770–2.
12. Cook JD, Finch CA. Assessing the iron status of a population. *Am J Clin Nutr* 1979;32:2115–9.
13. Torún B, Viteri FE. Tratamiento de niños hospitalizados con desnutricion proteinico-energetica severa. *Rev Col Med (Guatemala)* 1976;27:42–62.
14. Solomons NW, Torún B, Caballero B, Flores-Huerta S, Orozco G. The effect of dietary lactose on the early recovery from protein-energy malnutrition. I. Clinical and anthropometric indices. *Am J Clin Nutr* 1984;40:591–600.
15. Ramsay WNM. The determination of iron in blood plasma or serum. *Biochem J* 1953;53:227–31.
16. Addison GM, Beamish MR, Hales CN. An immunoradiometric assay for ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *J Clin Pathol* 1972;25:326–9.
17. Miles LEM, Lipschitz DA, Bicker CP, Cook JD. Measurement of serum ferritin by a 2-site immunoradiometric assay. *Ann Chem* 1974;61:209–24.
18. Clark LC, Thompson HL. Determination of creatine and creatinine in urine. *Clin Chem* 1949;21:1218–21.
19. Viteri FE, Alvarado J. The creatinine-height index: its use in the estimation of the degree of protein depletion and repletion in protein calorie malnourished children. *Pediatrics* 1970;46:696–706.
20. Siimes MA, Addiego JE Jr, Dallman PR. Ferritin in serum: diagnosis of iron deficiency and iron overload in infants and children. *Blood* 1974;43:581–90.
21. Dawson KP, Whimster J. Serum ferritin levels in iron deficient children. *NZ Med J* 1980;92:96–7.
22. Viteri FE, Tuna V, Guzman MA. Normal hematological values in the Central American population. *Br J Haematol* 1972;23:189–204.
23. Lahey ME, Behar M, Viteri FE, Scrimshaw NS. Values for copper, iron and iron-binding capacity in the serum of kwashiorkor. *Pediatrics* 1958;22:72–9.
24. Fondu P. Marasmic kwashiokor anemia. II. Kinetic patterns. *Biomedicine* 1973;18:124–33.
25. Olson RE. The effects of variations in protein and calorie intakes on the rate of recovery and selected physiological responses in Thai children with protein-calorie malnutrition. In: Olson RE, ed. *Protein-calorie malnutrition*. New York: Academic Press, 1975:275–97.
26. Kondi A, MacDougall L, Foy H, Mehta S, Mbaya V. Anemias of marasmus and kwashiorkor in Kenya. *Arch Dis Child* 1963;68:267–75.
27. Edozien JC, Udeozo IOK. Serum copper, iron, and iron-binding capacity in kwashiorkor. *J Trop Pediatr* 1960; 6:60–4.
28. Adams EB, Scragg JN. Iron in the anemia of kwashiorkor. *Br J Haematol* 1965;11:676–81.
29. Adams EB, Scragg JN, Naidoo BT, Liljestrand SK, Cockram VI. Observations on the aetiology and treatment of anemia in kwashiorkor. *Br Med J* 1967;3:451–4.
30. Trowell HC. Pellagra in African children. *Arch Dis Child* 1937;12:193–212.
31. Trowell HC, Simpkiss MJ. Intramuscular iron in the treatment of the anemia associated with kwashiorkor. *Lancet* 1957;2:265–76.
32. Krause JR, Stolc V. Serum ferritin and bone marrow iron stores. I. Correlation with absence of iron in biopsy specimens. *Am J Clin Pathol* 1979;72:817–20.
33. Jacobs A, Miller F, Worwood M, Beamish MR, Wardrop CA. Ferritin in the serum of normal subjects and patients with iron deficiency and iron overload. *Br Med J* 1972;4:206–8.
34. Cook JD, Lipschitz DA, Miles LE, Finch CA. Serum ferritin as a measure of iron stores in normal subjects. *Am J Clin Nutr* 1974;27:681–7.
35. Caballero B, Solomons NW, Torún B. Inapplicability of the logarithmic regression equation for the factorial calculation of total body iron in preschool children (Letter). *Pediatr Res* 1983;17:519–20.
36. Lipschitz DA, Cook JD, Finch CA. A clinical evaluation of serum ferritin as an index of iron stores. *N Engl J Med* 1974;290:1213–6.
37. Jacobs A, Worwood M. Ferritin in serum: clinical and biochemical implications. *N Engl J Med* 1975;292:951–6.
38. Elin RJ, Wolff SM, Finch CA. Effect of induced fever on serum iron and ferritin concentration in man. *Blood* 1977;49:147–53.
39. Birgegaard G, Hallgren R, Killander A, Venge P, Wide L. Serum ferritin during infection. A longitudinal study in renal transplant patients. *Acta Med Scand* 1979;205:641–5.
40. Morgan EH. Transferrin and transferrin iron. In: Jacobs A, Worwood M, eds. *Iron in biochemistry and medicine*. New York: Academic Press, 1974:30–71.
41. Drysdale JW, Olafdettir E, Munro HN. Effect of ribonucleic acid depletion on ferritin induction in rat liver. *J Biol Chem* 1968;243:552–5.
42. Caballero B, Solomons NW, Torún B. Short-term variability of ferritin concentrations in serum of children with severe protein-energy malnutrition (Letter). *Clin Chem* 1983;29: 521–2.
43. Jacobs RA, Sandstead HH, Klevay LM. Utility of serum ferritin as a measure of iron deficiency in normal males undergoing repetitive phlebotomy. *Blood* 1980;56:786–91.
44. McKenzie D, Friedman R, Katz S, Lanzcowsky P. Erythropoietin levels in anemia in kwashiorkor. *S Afr Med J* 1977;4:1044–6.
45. The anemia of protein-calorie malnutrition and its response to dietary protein. *Nutr Rev* 1979;37:81–2.
46. Sandesai MK, Haquani AH, Rajeshvari V, Kaur J. Kwashiorkor. A clinico-haematological study. *Br Med J* 1963: 2:93–6.