Role of Cofactors in the Treatment of Malnutrition as Exemplified by Magnesium

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In the absence of appropriate amounts of metabolically important cofactors such as magnesium, replenishment of malnourished patients with protein and carbohydrate will exaggerate the underlying abnormality even though the primary deficiency is corrected. The malnourished patients cannot utilize the food substances provided unless they have within their cells commensurate amounts of all the necessary cofactors required for the metabolism of the food supplied. This therapeutic problem in malnutrition is illustrated by three different examples of clinical deterioration when caloric and vitamin replenishment have been undertaken in the face of magnesium deficiency.

INTRODUCTION

Magnesium as a cofactor has a pervasive role in the body economy. It is a cofactor in transphosphorylations with ATP thus affecting oxidative phosphorylation, synthesis of lipids, proteins, nucleotides, nucleic acids, and coenzymes, activation of formate, acetate, and sulfate, methyl group transfers, and muscle contraction. In protein synthesis, magnesium is involved in every step, e.g., activation of specific enzymes involved in synthesis, maintenance of macromolecular and ribosomal structural integrity and stability, and control of interactions among macromolecules. In addition magnesium is the functional activator of many specific enzymes such as alkaline phosphatase, adenosine triphosphatase, enolase, transketolase, etc. Clearly depletion of cellular magnesium is likely to have far-reaching consequences.

Magnesium deficiency has a variable effect on tissue magnesium stores, and the functional abnormalities that result may be out of proportion to the tissue depletion. Thus bone and muscle magnesium best reflect body depletion of magnesium. In the rat on a severe magnesium deficient diet, the bone magnesium is reduced by one-half within 2 wk, by three-fourths within 4 wk, and by five-sixths within 8 wk, after which it decreases very little. In contrast the liver and kidney magnesium concentration remains normal up to the point of death. This holds true for the cell as a whole as well as each of the major fractions into which the cell may be subdivided (microsomes, mitochondria, nucleus, and supernatant). Despite the normal concentration of magnesium in these cells, magnesium dependent enzymes such as transketolase are affected. The serum magnesium concentration is a relatively poor reflector of tissue depletion, and the red cell magnesium content is not much better. Therefore the clinical likelihood that magnesium intake has been poor or that excessive magnesium has been lost, as in chronic alcoholism, must often be used as a basis for magnesium repletion.

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PROBLEMS IN THE TREATMENT OF UNDERNUTRITION

My objective in this paper is to illustrate indirect but vital consequences of magnesium deficiency in malnutrition. Malnutrition implies selective deficiencies, and is to be distinguished from undernutrition. Undernutrition, as in pure starvation, involves a balanced loss of tissue substance with no evidence of selective deficiencies. There are no clinical evidences of vitamin deficiencies or magnesium deficiency. However in pure starvation, as in malnutrition, there are serious consequences if the starved individuals are refed too rapidly. This became painfully evident at the end of World War II, when the concentration camp victims were brought back to allied hospitals for rehabilitation. Indiscriminate and uncontrolled refeeding led to fatalities that were never explained. However the importance of controlled refeeding became quickly apparent.

This unfortunate experience with the starvation victims of World War II was never studied quantitatively as a biologic phenomenon, and was a forgotten episode, when intravenous hyperalimentation was introduced as an effective form of nutritional rehabilitation of patients who could not eat. As a consequence, relatively large caloric loads were given comparatively rapidly to undernourished patients, and paresthesias, convulsions, coma, and death occurred in some instances (1)—a repetition of the experience of World War II. I recognized the connection, and an experimental study of this fatal hyperalimentation syndrome was undertaken in our hospital by Silvis and Paragas (2) who reproduced the phenomenon in chronically starved rats and dogs. They observed a mortality rate of 60% when chronically starved rats were infused with approximately 200 cal/kg/day, mostly carbohydrate. Doubling the calories raised the mortality to 100%. More cautious presentation of calories and stepwise increments in load eliminated the syndrome. The basis for this syndrome has not been established, though the clinical manifestations are consistent with a cellular deficit of magnesium. The extremely large carbohydrate load given the starved animals or patients abruptly raises the requirement for magnesium as a cofactor, and a relative cellular deficit probably occurs because the magnesium provided in the infusion is firstly insufficient to compensate for the cellular loss during starvation and secondly does not enter the cell as readily or as rapidly as the glucose.

PROBLEMS IN THE TREATMENT OF MALNUTRITION

In malnutrition there are also serious consequences if calories are provided as part of treatment without supplying necessary cofactors such as magnesium. In this case the specific therapeutic role of magnesium has been demonstrated. I will illustrate this with three different examples.

Example 1: Precipitation of symptoms of magnesium deficiency by providing calories without commensurate amounts of magnesium. The following case illustrates this phenomenon. The patient was a 64-year-old chronic schizophrenic with known valvular heart disease who had previously had an episode of congestive heart failure and pulmonary emboli. He was admitted on 3/13. One year previously he had been studied for fever of unknown origin, but no cause was identified. He was alert and oriented, but had a flat affect. He was emaciated, but was otherwise normal on physical and neurologic examination, except for the known aortic stenosis. An occult malignancy was initially suspected. His blood hemoglobin was 13.5 g/100 ml, white cell count 10,600/mm³ with 90% polymorphonuclears, and sedimentation rate 80 mm/hr. Sodium was 124 and potassium 2.9 mEq/liter. The
BUN was 14% mg%, serum albumin 2.0 g%, calcium 7.2 mg%, and phosphorus 2.1 mg%. An extensive evaluation for an occult malignancy including GI series, barium enema, and intravenous pyelogram was normal. X-rays of chest and bone were also normal. An electrocardiogram showed first degree A-V block and nonspecific ST-T wave changes.

After 1 mo of evaluations a low grade fever recurred which went unexplained, all relevant studies being negative. He received a course of tetracycline without effect. On 4/17 a program of tube feeding began and he received 2000 cal per day of a homogenized meal. Seven days later he was noted to be disoriented and to have “twitching and jerking movements.” These became more severe over a period of 2 days when he had “twitches and tremors of the entire body.” This was recognized as magnesium deficiency the next day, 10 days after the tube feedings were begun, despite the report of a serum magnesium concentration of 1.9 mg%. The patient at this time was dehydrated and had a BUN of 99 mg%. A videotape recording of his neuromuscular abnormality was made, which was later easily recognized as magnesium deficiency by individuals aware of this entity. He was started on an intravenous infusion of MgSO4. By the time he received 2 g his twitching had decreased, and with 3 g more all extraneous movements had disappeared. These infusions covered a span of approximately 36 hr. Though he no longer had manifestations of magnesium deficiency, the patient’s underlying disease progressed over the next month and he died in congestive heart failure due to acute rheumatic fever (diagnosed at autopsy).

While the underlying disease that led to his anorexia and emaciation was obscure prior to death, the neuromuscular abnormality precipitated by the tube feeding was readily recognized and eliminated by supplying extra magnesium. We had no measure of the extent of his body magnesium deficit at the time tube feedings were begun. Presumably it was of such magnitude that he lacked metabolically available magnesium to cope with the caloric load that had to be processed. The result was increased cellular demands that could not be met and his deficiency became symptomatic.

**Example 2: Deterioration and death of malnourished Nigerian children who were hospitalized and treated (Caddell).** Before the study of Joan Caddell in 1964, (3) it was common for Nigerian children with Kwashiorkor or Marasmus to deteriorate progressively or die suddenly while being replenished with high protein milk, multivitamins, iron, and potassium. These children were very sick with multiple problems including serious infections they could not cope with. Despite tremendous “noise” factors, i.e., nonmagnesium-related factors that could of themselves contribute significantly to deterioration and death, Caddell was able to show under controlled conditions that most of these children could be saved by adding magnesium replacement to the therapy.

Before turning to the details of her experiment, it is instructive to look at an illustrative case: The patient was a 2.5-yr-old extremely malnourished boy who had diarrhea for 1 mo. After receiving milk, vitamins, electrolytes, and antibiotics for 3 wk he was worse than on admission to the clinic. His temperature was 94.6° F, pulse 140 per minute, systolic blood pressure 54 mmHg. He could not eat. He was hydrated and started on magnesium sulfate. Within 12 hr his temperature was 97° F and systolic blood pressure 94 mmHg. By 70 hr his vital signs were stable and he had begun to eat. Fever and cough became apparent at this time and a chest x-ray revealed pneumonia. Pharyngeal cultures were positive for Staphylococcus aureus and Pseudomonas. On the fourth day he weighed 7.8 kg (17 lb). By the sixth day he
could sit up and drink from a cup, and on the eleventh day he was afebrile and could laugh and play. He went home on the thirteenth day, but could not walk with support until the third week, at which time he weighed 9.3 kg (20.5 lb). By 2 mo he could walk well but had poor muscle tone. At this time he weighed 11.25 kg (25 lb). After 7 mo, when he appeared normal, he weighed 14.54 kg (32 lb). The patient’s appearance at various times after start of magnesium therapy can be seen in Fig. 2 of a paper published by Caddell in 1969.(4)

Caddell’s controlled experiment (3) involved 52 patients of which 36 were critically ill and 16 seriously ill. The average age was 3.2 yr, weight 8.1 kg (18 lb), blood hemoglobin 9.2 g%. The total serum protein was less than 4.1 g% in three-fourths, and the serum sodium and serum potassium less than 125 and 2.5 mEq/liter, respectively, in one-third. The following symptoms and signs were observed:

- Emaciation, Severe Weakness, Anorexia, or Peripheral Edema in 75–100%
- Tachycardia, Lethargy, Major Skin Lesions, Severe Diarrhea, or Dehydration in 65–75%
- Hyperirritability, Cheilosis, or Pneumonia in 35–50%
- Hypothermia, Hypotension, Tremors, Ophtalmoplegia, or Nystagmus in 13–23%

All patients received repeated small feedings of an evaporated milk formula, 15 cal per ounce, intravenous infusions of electrolyte solutions, and nutritional supplements (three or four times daily) consisting of vitamins (thiamine 1 mg, riboflavin 1 mg, niacin 10 mg, pyridoxine 0.5 mg, ascorbic acid 25 mg, vit A 4000 units, vit D 666 units, and folic acid 5 mg) and KCl 0.5 g. Antibiotics were given where indicated. Those receiving magnesium were given MgSO4 4–6 mEq intramuscularly every 12 hr.

The early signs of a response to treatment were the return of the subnormal temperature and blood pressure to normal, the disappearance of anorexia, the alertness and mobility of the child, the return of a normal sleep pattern, and after the third day the presence of a diuresis, fever, cough, a loud cry, and beginning healing of skin lesions. The causes of death were pneumonia, general sepsis, and complications of severe gastroenteritis.

Of the 26 cases receiving magnesium, 4 died early (1 before receiving the magnesium), 3 died of sepsis with no evidence of improvement, 2 died of infection by the 10–15th day though showing some improvement, and 17 recovered, many dramatically. Of the 26 cases not receiving magnesium, 2 made excellent recoveries, 3 died early, and 21 deteriorated rapidly so the code was broken and magnesium therapy started since a fatal outcome was predictable. Of those then treated with magnesium, 4 died within 24 hr, 4 improved but died of sepsis, and 13 recovered dramatically.

This experiment made it clearly evident that magnesium replacement in these very sick children was life-saving. The magnesium permitted the utilization of food substances and vitamins that were abruptly supplied. In the absence of this co-factor, the caloric load exacerbated the illness leading to rapid deterioration despite the presence of needed protein, electrolytes, and vitamins.

Example 3: Vitamin unresponsiveness (5). This is a state of vitamin deficiency that fails to respond to vitamins supplied in adequate amounts. Though mostly unrecognized, this phenomenon is quite common among alcoholics. I will present two illustrative cases:

Case I. A 31-yr-old bartender, who sampled his wares excessively, was admitted
in severe congestive heart failure with dyspnea and edema. He had paresthesias of fingers and toes, an enlarged liver, and normal reflexes. A diagnosis of alcoholic cardiomyopathy was made. He was critically ill during his entire period of hospitalization. On the first day he developed frank pulmonary edema. He was treated with digoxin and diuretics as well as large parenteral doses of B-complex vitamins, particularly thiamine, 120 mg per day. Delirium tremens developed on the fourth day and lasted 1 wk. There was no objective evidence then of peripheral neuritis. The ankle jerks, which were present on admission, were absent the next day. Hypoesthesia of the feet and diminished vibration over the ankles appeared at this time. A frank foot drop suddenly became apparent on the eleventh day. Though the progression of the neuropathy was inadequately documented, the end result—a frank foot drop—occurred despite the presence of an excess of circulating thiamine from the beginning.

Case 2. This 46-yr-old alcoholic laborer had been working until 3 days before admission. His diet had been poor; he was anorexic, weak, and developed diarrhea. His hands and feet had become numb and tingled. He stopped working because his feet became so sensitive and painful to touch. On examination his mental state was normal. His hands and feet were extremely sensitive to touch, but he had hypesthesia over his legs. His reflexes were depressed. Blood hemoglobin was normal, and his sedimentation rate was 51 mm/hr. BSP retention was 35%, however his serum proteins, bilirubin, and prothrombin time were normal.

From the beginning he received large parenteral injections of thiamine and niacin (120 and 200 mg per day, respectively). Despite this the peripheral neuropathy progressed. Knee jerks disappeared. By the tenth day, he had a bilateral foot drop. His diarrhea had persisted. At this time a dermatitis of the face and perioral region first appeared which was characterized by peeling, cracking, and dark pigmentation. Subsequently he had rapid alopecia and formation of plaques with crusting on his hands. On the 23rd day he was seen by a dermatologist, who diagnosed pellagra resistant to vitamin therapy. By the 30th day he was nearly bald.

His neuropsychiatric status deteriorated steadily such that by the 38th day he had paresis, numbness, and marked tenderness of all extremities; inability to speak, obey simple commands, or feed himself; and incontinence of bowel and bladder. At this time the pellagrous dermatitis began to improve, and the diarrhea to subside. By the 66th day his hair had regrown and his skin had noticeably improved. The neurologic state was also improved. He could repeat phrases, state his name, and push himself around in a wheelchair. Reflexes had returned in his lower extremities. A pneumoencephalogram on the 80th day showed cortical atrophy. This finding and the dementia were thought to be due to alcoholism complicated by pellagra. He was discharged on the 98th day to a state mental hospital.

Despite the daily injection of large amounts of B-complex vitamins, particularly thiamine and niacin, this patient, who presented with early signs of a neuropathy, went on to develop a complete bilateral foot drop and a classic picture of pellagra. His liberal food consumption after hospitalization, especially carbohydrate, increased his need for thiamine and niacin which he apparently was unable to utilize. Though he had been able to work as a laborer up until 3 days before hospitalization, his illness resulted in permanent brain damage, and he had to be committed to an institution.

The two preceding cases illustrate the progression of signs of vitamin deficiency despite adequate provision of the appropriate vitamins. In a third similar type of
patient the progression of the neuropathy seemed to be "nipped in the bud" and the process reversed. This patient had received vigorous Mg²⁺ replacement on the assumption that deficiency of magnesium prevented the thiamine from being effective. While we suspected that the effect of the magnesium given was more than coincidental, what was clearly needed was a controlled study that evaluated the role of magnesium deficiency on the response of thiamine-deficient subjects to thiamine. We therefore performed such a controlled study in thiamine-deficient rats.

**Controlled study of the effect of magnesium deficiency on the response of thiamine-deficient animals to thiamine** (6, 7). The structure of the experiment is shown in Fig. 1. Rats placed on a thiamine-free diet cannot live much longer than 30 days. Nine groups of Holtzman female rats, eight to nine rats per group, were studied in the first experiment. Their average initial weight was 105 g. Group 1 was a control group (C), which was observed for 31 days, as indicated by the horizontal line. Group 2 received the same diet as the controls except for the absence of thiamine. These thiamine-deficient (Td) rats were sacrificed on the 31st day when they were preterminal. Group 3 (Td+T) were similar Td animals that received intraperitoneal injections of thiamine (as the hydrochloride) in five divided doses daily for 1 wk before they were sacrificed. Group 4 (TdMd) received a diet deficient in both thiamine and magnesium for 31 days. Group 5 (TdMd+T) were thiamine- and magnesium-deficient rats that received thiamine as indicated before sacrifice. Group 6 (TdMd+TM) were thiamine- and magnesium-deficient rats that received both thiamine and magnesium (as MgSO₄) before sacrifice. Group 7 (Md33) were animals on the magnesium-deficient diet for 33 days. Group 8 (Md59) were on the magnesium-deficient diet for 59 days. Group 9 (S) were rats that received the control diet for 20 days, whereafter all food was taken away. They were sacrificed after 7 days of starvation.

A second set of rats that received 10% alcohol in the daily drinking water was studied similarly. This normally provides approximately 20% of calories as alcohol. The average initial weight of these animals was 136 g.

The diet of the magnesium-deficient animals contained 32 µg of magnesium per gram of diet, as compared to 950 µg per gram for the control and thiamine-deficient diets. The therapeutic doses of both thiamine and MgSO₄ were very large. Thiamine undoubtedly moved into the cell rapidly. Magnesium, by contrast, is known to penetrate the cell membrane slowly, and most of the magnesium given was probably excreted, only a small unknown fraction being available to the cell.

![Graph](image_url)

**FIG. 1.** Plan of the first experiment evaluating the effect of magnesium deficiency on the response of thiamine-deficient rats to repletion with thiamine. Thiamine replacement was as thiamine HCl (5 mg/day × 7), magnesium as MgSO₄ (125 mg/day × 7).
The variables measured were growth, liver and whole blood transketolase activity, liver and whole blood thiamine and magnesium concentrations, liver nitrogen content and liver transaminase activity, both GOT and GPT. Transketolase is an enzyme of the pentose shunt which requires thiamine pyrophosphate and Mg$^{2+}$ as cofactors. Its activity was measured as the amount of sedoheptulose formed per hour per milliliter of blood or per half-hour per gram dry weight of liver from a substrate mixture containing ribose-5-phosphate (7).

**Effect on body growth.** The overall effect of thiamine deficiency, with and without coexistent magnesium deficiency, on growth and on the response to replacement therapy is shown in Fig. 2. The vertical lines in this and in all subsequent charts represent the range of values about the average. Prior to replacement therapy, marked by the asterisks, growth of the Td and TdMd rats was similar. The alcohol-fed rats had a greater tolerance for the thiamine-deficient state, as is well known, and survived 3 wk longer as a rule. Growth in purely magnesium-deficient rats, not shown in the figure, was 90% of normal in those not receiving alcohol and 75% of normal in those receiving alcohol (6).

In response to thiamine given over a period of only 1 wk, the Td rats of the first experiment (no alcohol) increased their body weight by 50%, approaching the weight of the controls. The presence of magnesium deficiency limited this response to 14%. Addition of MgSO$_4$ to the therapy with thiamine augmented the response of TdMd rats so they increased their weight by 39%. The differences among these responses were statistically significant. The corresponding increments in the alcohol-fed animals were 57, −4, and 30%, respectively.

![Graph showing growth response to thiamine or to thiamine and magnesium of thiamine-deficient or thiamine- and magnesium-deficient rats.](image)

**FIG. 2.** Growth response to thiamine or to thiamine and magnesium of thiamine-deficient or thiamine- and magnesium-deficient rats. The alcohol groups received 10% ethyl alcohol in the drinking water. C, represents the average growth curve of each respective control group. The asterisks indicate the point at which replacement therapy was begun. The vertical lines represent the ranges about the means in this and all subsequent charts. (Adapted from article in *J. Lab. Clin. Med.* 72, 261–267, 1968. Reproduced with permission of The Mosby Company).
The substantial growth response to the addition of magnesium salts in therapy was somewhat surprising, considering the known difficulty with which magnesium traverses the cell membrane and the absence of such a response in the case of liver transketolase, to be shown below. In bone and muscle, at least, the ion was apparently used readily in protein synthesis and enzyme activation processes.

**Effect on liver transketolase (TK).** In the first experiment (Fig. 3), liver TK was decreased by 70–80% in the Td and S animals (shown at positions Nos. 2, 4, and 9). It was reduced by an equivalent amount in pure Md (Nos. 7 and 8). The Td rats responded to thiamine by rebounding above the control level (No. 3). When Md was also present, the response to thiamine was incomplete (No. 5), being about one-half of that observed in the absence of Md (No. 5 vs 3). The probability was less than 1 in 1000 that such a difference would occur by chance. The addition of MgSO₄ to the therapy (No. 6) had no immediate effect. The entire pattern of changes was similar in the rats ingesting alcohol.

That the marked reduction of TK activity in Td and in Md is not due to simple undernutrition, is evident in the results of a pair-fed experiment (Fig. 4), in which each animal of the C, TdMd, and Md groups was fed the amount of food consumed by a corresponding animal of the Td group. The animals were sacrificed after 1 mo. The low TK activity values in pure Md shown in Fig. 3 could not, in any event, be attributed to undernutrition, since growth, liver weight, and liver nitrogen content in these animals were normal or nearly normal during the first month. There was also no similar decrease in the liver transaminases, GOT and GPT, which are not magnesium-dependent enzymes (Fig. 5).

Our conclusion from this study in rats was that in the presence of magnesium deficiency, thiamine deficient animals cannot utilize the thiamine that is provided. The implications for the analogous clinical circumstance seem fairly evident.
SOME GENERALIZATIONS THAT SEEM JUSTIFIED

Malnourished patients cannot utilize food substances provided, unless they have available within their cells commensurate amounts of the necessary cofactors required for the metabolism of the food substances supplied. Replacement of deficient factors such as vitamins without first providing the necessary cofactors will be ineffective. Furthermore, in the absence of the required cofactors, sudden loads of protein and carbohydrate will exaggerate the underlying abnormality even though the primary deficiency is corrected. Since cofactor replenishment is not easily and rapidly achieved, caloric replenishment in severely malnourished patients should be a gradual process.

Magnesium deficiency of modest degree is probably very common in association with a variety of diseases, and this deficiency is ordinarily inadequately reflected by the serum (or red cell) concentration of magnesium. Whenever there is evidence of loss of intracellular elements such as potassium or phosphorous, it is a good practice to supply magnesium along with the depleted element. Magnesium repletion is a slow process since much that is given at any given time does not get into tissue cells and is excreted. The physician must therefore be vigorous and persistent in his efforts to correct intracellular deficits of magnesium.

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