

- Maycock, W. d'A., Evans, S., Vallet, L., Combridge, B., Wolf, P., McGibbon, N., French, E. E., Walleit, L. H., Dacie, J. V., Biggs, R., Handley, D., and Macfarlane, R. G. (1963). Further experience with a concentrate containing human anti-haemophilic factor. *British Journal of Haematology*, **9**, 215.
- Miller, W. V., Holland, P. V., Sugarbaker, E., Strober, W., and Waldmann, T. A. (1970). Anaphylactic reactions to IgA: a difficult transfusion problem. *American Journal of Clinical Pathology*, **54**, 618.
- Mollison, P. (1967). *Blood Transfusion in Clinical Medicine*, 4th ed., p. 542. Blackwell Scientific Publications, Oxford and Edinburgh.
- Prentice, C. R. M., Izatt, M. M., Adams, J. F., McNicol, G. P., and Douglas, A. S. (1971). Amyloidosis associated with the nephrotic syndrome and transfusion reactions in a haemophilic. *British Journal of Haematology*, **21**, 305.
- Rizza, C. R., and Biggs, R. (1971). Haemophilia today. *British Journal of Hospital Medicine*, **6**, 343.
- Rizza, C. R., and Matthews, J. M. (1972). Management of the haemophilic child. *Archives of Disease in Childhood*, **47**, 451.
- Schmidt, A. P., Taswell, H. F., and Gleich, G. J. (1969). Anaphylactic transfusion reactions associated with anti-IgA antibody. *New England Journal of Medicine*, **280**, 188.
- Vyas, G. N., Perkins, H. A., and Fudenberg, H. H. (1968). Anaphylactoid transfusion reactions associated with anti-IgA. *Lancet*, **2**, 312.

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Addendum

Since this report was written, 3 haemophiliacs have been reported to develop pulmonary oedema after transfusion of fresh frozen plasma and 1 of them died. 1 received a transfusion containing white cell antibodies and another Gm antibodies (Kernoff *et al.*, 1972).

REFERENCE

- Kernoff, P. B. A., Durrant, I. J., Rizza, C. R., and Wright, F. W. (1972). Severe allergic pulmonary oedema after plasma transfusion. *British Journal of Haematology*, **23**, 777

Magnesium supplementation in Bartter's syndrome

Bartter's syndrome (hypokalaemic, hypochlorhaemic alkalosis, normotension, growth failure, and juxtaglomerular hyperplasia) is a rare disorder with less than 25 reported cases (Sutherland *et al.*, 1970). There appear to be two forms of this syndrome. The mild form usually has its onset after the first year of life, presenting with electrolyte imbalance, growth failure, and weakness, and markedly improves with electrolyte correction

(Beilin *et al.*, 1967; Cannon *et al.*, 1968; Greenberg *et al.*, 1966). Those with the severe type have symptoms of lethargy, poor appetite, dehydration, seizures, failure to thrive from the early months of life, and usually succumb before 1 year of age (Sutherland *et al.*, 1970; Walker, 1971). This report describes the apparent life-saving effects of magnesium supplementation in an infant with the severe form of Bartter's syndrome.

Case report

An 11-week-old Black infant was admitted because of failure to thrive. He had been the 2.62 kg product of a term pregnancy. His unwed mother reported her gestation and delivery to have been uncomplicated. A 4-year-old half-brother and a 15-month-old sister are healthy. He had been apathetic, eating poorly, regurgitating, and had failed to gain weight from 3 weeks of age. On admission he weighed only 2.79 kg with a height of 54 cm. He was emaciated, apathetic, mildly febrile, and sweating. He showed severe muscle weakness and had essentially no head control, deep tendon reflexes were hypoactive, and there was no muscle twitching. Serum electrolytes showed him to have marked hypokalaemic, hypochlorhaemic alkalosis with a serum sodium 133 mEq/l., potassium 2.0 mEq/l., chloride 74 mEq/l., total carbon dioxide 40 mEq/l., and pH 7.62. The serum calcium, phosphorus, creatinine,

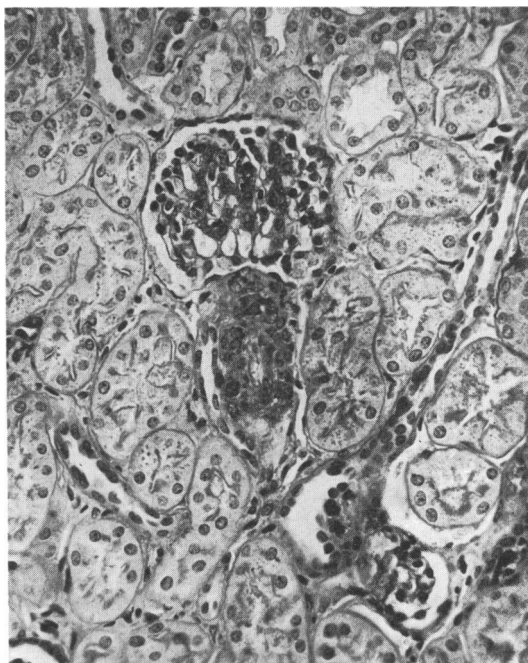


FIG.—Renal biopsy showing cloudy swelling of the proximal tubules and juxtaglomerular hyperplasia. ($\times 129$)

amino acids, proteins, creatine phosphokinase, and a barium swallow were all normal. The 24-hour urinary excretions of potassium, sodium, and chloride were excessive in respect to serum electrolytes and exceeded dietary intake. Total body potassium as determined by the natural isotope method was found to be 25% below normal. Results of 11 serum magnesium determinations on different days ranged from 1.5 to 1.9 mEq/l. with a mean of 1.7 mEq/l. His blood urea-nitrogen ranged between 30 and 40 mg/100 ml, and an ^{125}I iodotholamide clearance was $39 \text{ cm}^3/\text{min}$ per 1.73 m^2 (normal adult range 90 to $120 \text{ cm}^3/\text{min}$ per 1.73 m^2). IVP showed delayed visualization bilaterally. Renal biopsy (Fig.) showed cloudy swelling of the proximal tubules and marked hyperplasia of the juxtaglomerular apparatus. Plasma renin activity and aldosterone levels were raised fifteen- to fifty-fold on repeated determinations, though at no time was the patient hypertensive.

A diagnosis of Bartter's syndrome was made and the subject was started on oral potassium chloride supplementation. In spite of correction of serum electrolytes and adequate caloric intake (140 to 160 cal/kg per 24 hours achieved by gavage) he continued to grow poorly, remained apathetic, hypotonic, and refused to eat. There was no clinical improvement after the addition of either supplemental sodium chloride or a combination of both sodium chloride and spironolactone (12.5 mg twice daily) to his diet; however, subsequent plasma renin and aldosterone levels fell conspicuously but remained raised (Table). Consequently, a muscle biopsy was performed and sodium and magnesium content estimated. The sodium was 91 mEq/kg fat-free wet weight (normal 33-43) and the magnesium was 11.6 mEq/kg fat-free wet weight (normal 20 ± 1.8).

Because of the diminished muscle magnesium content, he was started on oral magnesium oxide therapy at a dosage of 30 mg MgO/kg body weight per day (6 mEq Mg/day). Within 48 hours, he showed a marked improvement in muscle tone and strength, good head control, and improved appetite, so that he no longer required gavage feedings. He gained weight at a rate of 25 g/day over the next 19 days and then reverted to his previous weight gain velocity of 10 g/day. The mean serum magnesium level increased to 1.9 mEq/l. during

the succeeding 6 weeks. Statistically, this level was significantly higher than the mean serum magnesium level before therapy ($P < 0.01$). His mental and motor functions improved dramatically as reflected by advancement in developmental milestones.

At 9 months of age he developed an intercurrent enteritis and magnesium oxide was discontinued for 3 days. During this interval, the other electrolyte supplementations were continued and normal serum electrolyte values were maintained; however, he became hypotonic, unable to sit, apathetic, and refused to eat. After the reinstatement of magnesium oxide therapy there was again rapid improvement in his appetite and motor tone. A repeat muscle biopsy at 10 months of age showed a normal magnesium concentration (19.8 mEq/kg fat-free wet weight) but no change in the sodium content. Now at 16 months he is progressing satisfactorily on magnesium 30 mg/kg per 24 hours, potassium chloride 28 mEq/24 hours (both given in divided dosage 4 times daily), and spironolactone 12.5 mg twice daily.

Discussion

Hypomagnesaemia has not been a consistent feature of Bartter's syndrome, and was not observed at any time in the present case. However, a total body depletion of magnesium, with a decrease in intracellular concentrations, can occur in the presence of normal serum levels (MacIntyre *et al.*, 1961; Martin, 1969). The use of supplemental magnesium in Bartter's syndrome with hypomagnesaemia has previously been described by Sutherland and co-workers (Sutherland *et al.*, 1970) in two subjects who died before the influence of this therapy could be ascertained. Hyperaldosteronism is associated with excessive urinary excretion of magnesium, and a negative balance for this element (Wacker and Parisi, 1968; Horton and Biglieri, 1962); therefore, patients with Bartter's syndrome may be at particular risk from magnesium deficiency. Measurements of muscle magnesium in Bartter's

TABLE

Effect of 14 days of the following electrolyte supplementations on plasma renin activity (PRA) and aldosterone levels.

Dietary supplement	Plasma renin activity (ng/ml per hr)	Plasma aldosterone (pg/ml)	Serum	
			Na (mEq/l.)	K (mEq/l.)
None	750	8956	133	2.0
KCl	223	10,619	134	4.6
KCl + NaCl	125	4294	147	4.7
KCl + NaCl + MgO	137	1907	144	3.8
KCl + NaCl + MgO	84	1503	140	4.1

Note: Normal adult fasting reclining PRA ranges from 0.2-3.6 ng/ml per hr, and normal adult fasting reclining aldosterone levels range from 32-200 pg/ml.

syndrome have not been reported previously; the low intracellular magnesium concentration found in this patient suggests that magnesium deficiency may be more common in Bartter's syndrome than indicated by serum magnesium levels alone.

Anorexia, apathy, and muscle weakness are common features of magnesium deficiency (Shils, 1969); all of these were present in our patient and improved after the introduction of dietary magnesium supplementation. The fever and excessive sweating also disappeared with magnesium supplementation. These are not recognized manifestations of magnesium deficiency; however, it is interesting to note that magnesium administration is effective in reducing the fever and sweating that occurs in patients with osteogenesis imperfecta (Solomons and Styner, 1969). Before the magnesium therapy, his progressive clinical course was in keeping with the severe type of Bartter's syndrome; now, at 16 months of age, he is progressing normally apart from a diminished growth velocity. This course is most unusual for subjects with the severe infantile type of disease. It is concluded that intracellular depletion of magnesium may be responsible for at least some of the severe features of this disease which do not respond to more conventional therapy, and that measurement of muscle magnesium and/or a prolonged trial of magnesium supplementation should be undertaken in all subjects with the severe type of Bartter's syndrome.

Summary

Intracellular magnesium deficiency, with normal serum magnesium levels, was shown in an infant with the severe type of Bartter's syndrome. After the introduction of oral magnesium therapy, there was marked improvement in appetite and in muscle tone and strength; the intramuscular concentration of magnesium increased to a normal level. At 16 months he was progressing normally apart from a diminished growth velocity, and has had an unusually prolonged survival. It is concluded that intracellular magnesium depletion may contribute to the clinical manifestations and fatal course of this disease.

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REFERENCES

- Beilin, L. J., Schiffman, N., Crane, M., and Nelson, D. H. (1967). Hypokalaemic alkalosis and hyperplasia of the juxtaglomerular apparatus without hypertension or oedema. *British Medical Journal*, **4**, 327.
- Cannon, P. J., Leeming, J. M., Sommers, S. C., Winters, R. W., and Laragh, J. H. (1968). Juxtaglomerular cell hyperplasia and secondary hyperaldosteronism (Bartter's syndrome): a reevaluation of the pathophysiology. *Medicine*, **47**, 107.
- Greenberg, A. J., Arboit, J. M., New, M. I., and Worthen, H. G. (1966). Normotensive secondary hyperaldosteronism. *Journal of Pediatrics*, **69**, 719.
- Horton, R., and Biglieri, E. G. (1962). Effect of aldosterone on the metabolism of magnesium. *Journal of Clinical Endocrinology and Metabolism*, **22**, 1187.
- MacIntyre, I., Hanna, S., Booth, C. C., and Read, A. E. (1961). Intracellular magnesium deficiency in man. *Clinical Science*, **20**, 297.
- Martin, H. E. (1969). Clinical magnesium deficiency. *Annals of the New York Academy of Sciences*, **162**, 891.
- Shils, M. E. (1969). Experimental human magnesium depletion. *Medicine*, **48**, 61.
- Solomons, C. C., and Styner, J. (1969). Osteogenesis imperfecta: effect of magnesium administration on pyrophosphate metabolism. *Calcified Tissue Research*, **3**, 318.
- Sutherland, L. E., Hartroft, P., Balis, J. U., Bailey, J. D., and Lynch, M. J. (1970). Bartter's syndrome. A report of four cases, including three in one sibship, with comparative histologic evaluation of the juxtaglomerular apparatuses and glomeruli. *Acta Paediatrica Scandinavica*, **Suppl. 201**, 1.
- Wacker, W. E. C., and Parisi, A. F. (1968). Magnesium metabolism. *New England Journal of Medicine*, **278**, 712.
- Walker, S. H. (1971). Severe Bartter's syndrome in Blacks. *New England Journal of Medicine*, **285**, 1150.

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Generalized hypermobility of joints

Arthrochhalasis multiplex congenita

Generalized hypermobility of joints has been reviewed by Hass and Hass (1958) who described 5 patients in detail and called the condition arthrochhalasis multiplex congenita; they noted that little attention had been paid previously to the orthopaedic manifestations and stressed that generalized hypermobility could exist without skin laxity; they suggested that it was an entity separable from Ehlers-Danlos syndrome and that joint involvement was very variable.

Carter and Sweetnam (1960) showed the strong