Plasma magnesium in health and disease

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SYNOPSIS Simpler and more accurate flame spectrophotometric techniques are now available for estimating magnesium. Because of the development of modern electrolyte therapy, cases of hypomagnesaemia are now encountered more frequently. The condition may lead to dangerous convulsions without sufficient warning. Some causes of hypomagnesaemia and hypermagnesaemia are presented.

Studies of plasma magnesium levels have not yet been widely introduced to the field of routine clinical chemistry. However, two factors have aroused interest in studying the plasma level of this element in recent years. 1, Just as the adoption of therapeutic measures for treating dehydration and disturbances of sodium metabolism in the past revealed cases of hypokalaemia and emphasized the importance of studying plasma potassium, so the treatment of disturbances of potassium, sodium, and calcium metabolism is now unmasking cases of hypomagnesaemia. 2, The old methods of estimating magnesium, which were either cumbersome or inaccurate, are now superseded by simple flame-photometric techniques.

Magnesium deficiency has been thoroughly studied in rats. Briefly this condition results in peripheral vasodilatation, convulsions, a rise in plasma calcium, and nephrocalcinosis (MacIntyre and Davidsson, 1958).

The condition has also been reported in man. Because it is usually associated with multiple electrolyte and nutritional deficiencies the syndrome is not yet clearly defined. However, convulsions, which may be fatal, have been reported (Hanna, Harrison, MacIntyre, and Fraser, 1960).

Using simple and accurate flame spectro-photometric techniques, magnesium metabolism was studied in about 100 subjects at the Hammersmith Hospital, London, over the last three years. In this paper an attempt is made to summarize and discuss the plasma magnesium findings in some of them.

MATERIAL AND METHODS

Subjects were studied in the metabolic unit. The balance technique and analytical methods have been reported elsewhere (Hanna *et al.*, 1960). Plasma magnesium was determined by the method described by Alcock, MacIntyre, and Radde (1960) and involved diluting 10 times with a deproteinizing fluid and interpolating flame-spectrophotometric emission of the supernatent between suitable standards. The flame-spectrophotometer used was a Zeiss P.M.Q. II spectrophotometer[2] with a flame attachment and a double monochromator.

RESULTS AND DISCUSSION

NORMAL LEVEL AND RANGE Fig. 1 shows the mean plasma magnesium levels of 12 normal healthy laboratory workers. A histogram showing plasma magnesium levels in 72 normal subjects as reported by Alcock *et al.* (1960) is also charted. It can be seen that the mean plasma magnesium level for normal subjects is 1·66 mEq./litre and that the range of normal is about 1·5 to 1·8 mEq./litre.

Table I summarizes the mean normal plasma magnesium level as reported by different authors. The differences between the mean values reported do not reflect a wide range for normal plasma magnesium. Studies in magnesium metabolism show that in health the body maintains the plasma magnesium level just as carefully as it does calcium (MacIntyre and Wootton, 1960). FitzGerald and Fourman (1956) put themselves on a magnesium-deficient diet (1·1 mEq. per day) for about four weeks and notwithstanding found no change in their plasma magnesium levels. Similar findings were reported by Walker and Walker (1936).

The differences between the means reported seem to be due to the fact that some authors used magnesium oxide as a standard. This substance is not suitable because it is difficult to prepare in a pure state and it absorbs carbon dioxide from the air;

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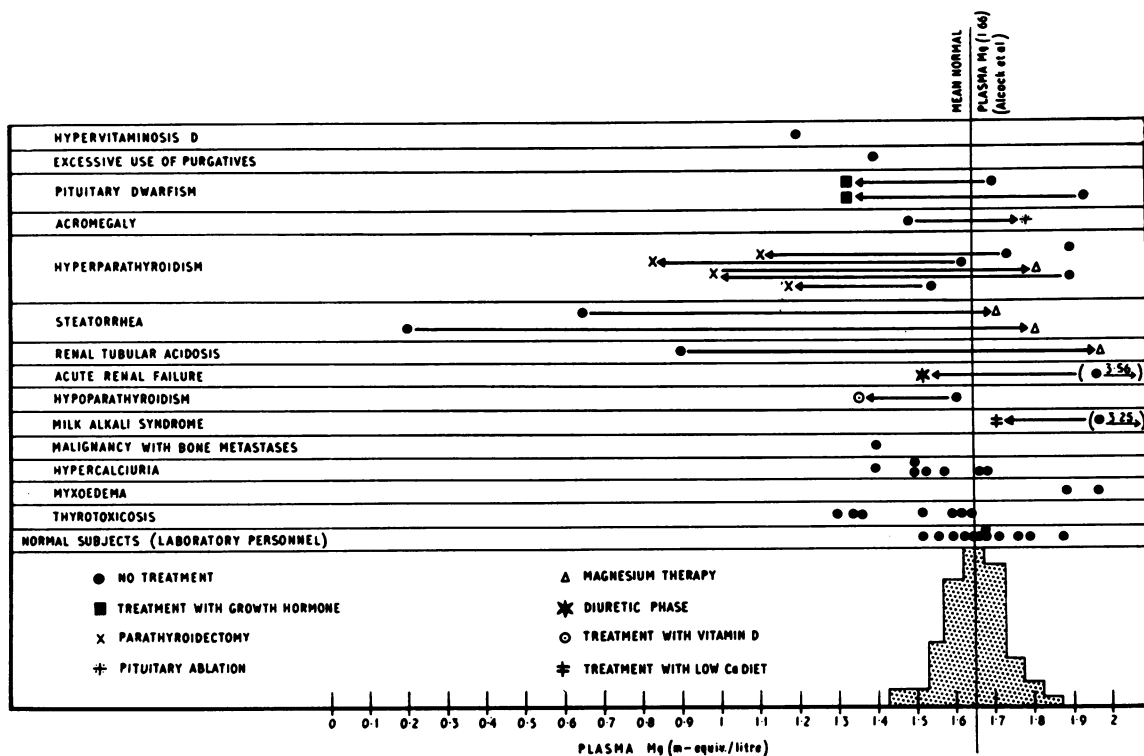[2] Carl Zeiss, Oberkochen, Germany.

FIG. 1

TABLE I

MEAN PLASMA MAGNESIUM LEVELS REPORTED BY VARIOUS
AUTHORS

Author	Method	Mean (mEq./l.)
Watchorn and McCance (1932)	P.P.	2·07
Hald (1933)	P.P.	1·70
Greenberg, Lucia, Mackey, and Tufts (1933)	H.P.	2·28
Schachter (1959)	F.	1·83
Hoffman (1937)	H.P.	1·82
Hirschfelder and Haury (1938)	T.Y.	1·76
Cope and Wolff (1942)	P.P.	1·66
Simonsen, Westover, and Wertman (1947)	P.P.	1·68
Silverman and Gardner (1954)	T.Y.	1·77
Davis (1955)	F.P.	1·66
Carr and Frank (1956)	E.D.T.A.	1·72
Wacker and Vallee (1957)	F.P.	2·05
Hunter (1958)	E.B.	1·69
Van Fossan, Baird, and Tekell (1959)	F.P.	1·67
Alcock et al. (1960)	P.F.	1·66

P.P. = phosphate precipitation methods
T.Y. = titan yellow methods
H.P. = hydroxyquinoline precipitation methods
F.P. = flame photometric methods
E.D.T.A. = titration with E.D.T.A.
E.B. = erichrome black methods
F = fluorimetric methods

heating to 900°C. is needed to decompose magnesium carbonate (Mellor, 1923). Using impure magnesium oxide heated to 110° or to 120°C., as some authors did (Wacker and Vallee, 1957), would produce high results.

HYPOMAGNESAEMIA Table II summarizes some of the wide variety of clinical conditions reported to be associated with hypomagnesaemia. However, before accepting some of these reports in terms of a causal relationship, certain points should be taken into consideration.

If liver cirrhosis is accepted as one of the causes of hypomagnesaemia (Flink, Konig, and Brown, 1955), it, in association with alcoholism (Flink, Stutzman, Anderson, Konig, and Fraser, 1954), may well be the result of the liver cirrhosis frequently associated with alcoholism. Also the reported association between idiopathic epilepsy and hypomagnesaemia (Haury and Cantarow, 1942) should be reinvestigated to see whether the subjects are genuinely idiopathic or are just hypomagnesaemic patients showing convulsions. Such considerations, however, do not alter the fact that hypomagnesaemia may result from certain clinical conditions, especially

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TABLE II

CLINICAL CONDITIONS REPORTED TO BE ASSOCIATED WITH
HYPOMAGNESAEMIA

Clinical condition	Authors
Hyperparathyroidism	
Pre-operative	Harmon (1956); Barnes, Crane, and Cope (1957)
Post-operative	Potts and Roberts (1958); Agna and Goldsmith (1958)
Primary aldosteronism	Mader and Iseri (1954); Milne, Muehrcke, and Aird (1957)
Gastrointestinal disturbances (malabsorption syndrome, vomiting, resection, etc.)	Hammarsten and Smith (1957); Card and Marks (1958); Randall *et al.* (1959); Vallee *et al.* (1960); Hanna *et al.* (1960); MacIntyre, Hanna, Booth, and Read (1961)
Osteolytic bone disease	Smith and Eliel (1956)
Idiopathic hypercalcaemia in infancy	Lowe, Henderson, Park and McGreal (1954)
Chronic glomerulonephritis	Martin *et al.* (1952); Randall *et al.* (1959)
Alcoholism	Flink, *et al.* (1954); Randall *et al.* (1959)
Liver cirrhosis	Flink *et al.* (1954)
Eclampsia, epilepsy, diabetes mellitus, bronchial asthma, malignancy, thyrotoxicosis	Haury (1940); Haury and Cantarow (1942)

gastrointestinal disturbances, and may be in itself hazardous to the patient's health.

Fig. 1 shows the means of plasma magnesium levels for 45 subjects studied; 12 of these were normal laboratory workers and the rest were selected because they were expected to show some disturbance in magnesium metabolism. Accepting the range of 1·5 to 1·8 mEq./1 as the normal range of plasma magnesium, 16 of these subjects were hypomagnesaemic or became hypomagnesaemic after certain therapeutic measures were taken. These cases of hypomagnesaemia (Fig. 1) are attributed to the following clinical conditions:

Clinical Condition	No. of Cases
Removal of parathyroid adenoma	4
Thyrotoxicosis	3
Steatorrhoea	2
Administration of vitamin D	2
Treatment with growth hormone	2
Renal tubular acidosis	1
Acromegaly	1
Excessive use of purgatives	1
Malignancy with bone metastases	1
Hypercalciuria (idiopathic)	1

These cases may be divided into two groups according to their aetiology. The first includes clinical conditions in which magnesium is lost from the extracellular fluid compartment to bone and soft tissues, and also removal of parathyroid adenoma and administration of vitamin D or growth hormone (Hanna, 1960, 1961; Hanna, Harrison, MacIntyre, and Fraser, 1961). Patients in this group may show a positive magnesium balance. The second group includes clinical conditions in which magnesium is lost from the body via the gastrointestinal tract and the kidneys. Here a negative magnesium balance is the cause of hypomagnesaemia. Cases of primary aedosteronism, steatorrhoea, idiopathic hypercalciuria, thyrotoxicosis, renal tubular acidosis, malignancy with bone metastases, and excessive use of purgatives fall into this group (Hanna *et al.*, 1960; Hanna and MacIntyre, 1960).

Clinical picture An understanding of the clinical picture of hypomagnesaemia is of importance to the clinician in order to be able to identify cases of hypomagnesaemia. Previously, such cases were not diagnosed, mainly because of the lack of suitable analytical techniques but partly because patients died, suffering from shock or dehydration, long before the development of hypomagnesaemia. But now, with the development of suitable analytical methods for magnesium, together with the advancements in the field of fluid and electrolyte replacement therapy and the development of modern surgical and medical life-saving techniques, cases of hypomagnesaemia are being discovered more frequently.

The syndrome of magnesium deficiency has been well studied in experimental animals (MacIntyre and Davidsson, 1958). In farm ruminants magnesium deficiency presents an economic problem, and its incidence in suckling calves has been placed as high as 5% in Great Britain (Blaxter and Sharman, 1955). The syndrome is characterized by convulsions. When it occurs in lactating cows it is sometimes called 'grass staggers'.

However, in man the syndrome is less clearly defined. Tetany, tremors, choreiform movements, fibrillary twitches, delirium, rigidity, confusion, status epilepticus, cerebellar symptoms, stupor, and athetoid movements are amongst the signs and symptoms reported in association with hypomagnesaemia in man. Of these, the most widely accepted is tetany and several textbooks describe 'hypomagnesaemic tetany' as a clinical entity (Duncan, 1952; Nelson, 1959). Despite this wide variety of signs and symptoms, Martin, Mehl, and Wertman (1952) failed to elicit any due to hypomagnesaemia in a study of a series of 16 patients with plasma magnesium levels less than 1 mEq./l. and they particularly emphasized the absence of tetany.

Confusion regarding tetany has arisen from two sources. Although the widely accepted definition is the development of peripheral painful carpopedal spasms, some authors have not distinguished between

TABLE III

SIGNS AND SYMPTOMS SOMETIMES ENCOUNTERED IN HYPOMAGNESAEMIA

Clinical Condition	Hospital No.	Plasma Mg. (mEq./l.)	Signs and Symptoms
Steatorrhoea	227935	0·2	Vertigo, muscle weakness, positive Chvostek's sign, low alkaline phosphatase, low voltage of E.E.G., ataxia, convulsions
Hyperparathyroidism (post-operative)	220252	1·0	Muscle weakness, mental disturbances
Renal tubular acidosis	199012	0·9	Positive Chvostek's sign, convulsions

convulsions and tetany (Vallee, Wacker, and Ulmer, 1960). The second source of confusion is that Kruse, Orent, and McCollum (1932), followed by Greenberg and Tufts (1938), used the term 'tetany' to describe the convulsions occurring in magnesium-deficient rats. The latter authors used the term, despite their recognition of the clear distinction between the neuromuscular disturbances produced by hypocalcaemia and those produced by hypomagnesaemia. They stated that 'magnesium tetany is of a definitely different type from low calcium tetany'. This use of one term for two distinct conditions has led to a search for hypomagnesaemia in patients suffering from all types of neuromuscular disturbances. It is hardly surprising, therefore, that low plasma magnesium was sometimes encountered, since most of these patients were suffering from multiple deficiencies (Randall, Rossmeisl, and Bleifer, 1959).

Even the control of tetany or any other neuromuscular disturbance by magnesium does not establish a causal relationship between magnesium deficiency and tetany. Harrison, Fraser, and MacIntyre (unpublished data) found that an intravenous infusion of magnesium may control tetany produced by hypocalcaemia in the presence of normal plasma magnesium levels.

The danger of accepting the reported signs and symptoms is the false sense of security in their absence. Out of the 16 cases of hypomagnesaemia presented in Fig. 1 only three showed signs and symptoms attributable to hypomagnesaemia (Table III). In two of them the earliest striking manifestation of hypomagnesaemia was an attack of epileptiform convulsions.

All the signs and symptoms listed in Table III were reversed by magnesium infusion. Except for the convulsive seizures, the other signs and symptoms were not striking.

The convulsive seizures In Case A (Table III), 12 days after admission the patient suddenly vomited and became confused and disorientated. Two convulsive epileptiform seizures followed. An intravenous infusion of 100 mEq. magnesium chloride in 1 litre 5% dextrose was given over the next four hours. During the day the confusion receded and a left homonymous hemianopia became evident along with some motor dysphasia, perseveration, and right-sided weakness and inattention. An E.E.G. showed changes suggesting a focal cerebral lesion. All these neurological signs gradually disappeared over the next five days. Subsequently, the patient had complete amnesia for the convulsive seizures and the day following them.

Case C (Table III), six days after admission, had a generalized epileptiform convulsion. An E.E.G. showed low voltage for all complexes. Chvostek's sign was positive. An intravenous infusion of 50 mEq. magnesium chloride was given over four hours. At the end of the infusion the patient remarked that she felt better and stronger. Chvostek's sign became negative and an E.E.G. taken 45 minutes after the end of magnesium infusion showed a definite increase in voltage of the Q.R.S. complex and T waves.

It is not possible, at this stage, to claim which of the signs and symptoms is due to hypomagnesaemia and which to magnesium deficiency in other compartments of the body. Muscle weakness and a low voltage in the E.C.G. could have resulted from intracellular magnesium deficiency. Radde, Hanna, and MacIntyre (unpublished data) found that magnesium-deficient rats show a low voltage in the E.C.G. when compared with normal controls.

These cases illustrate the mildness of the signs and symptoms in magnesium deficiency and show that very little warning is given before dangerous convulsions ensue.

HYPERMAGNESAEMIA Hypermagnesaemia was reported in cases of uraemia. Hamburger (1957) reported that clouding of consciousness associated with uraemia follows fairly closely the level of plasma magnesium.

In the present study (Fig. 1) a mild degree of hypermagnesaemia was encountered in two cases of myxoedema, in two cases of hyperparathyroidism with renal damage, and in one case of pituitary dwarfism. A severe degree of hypermagnesaemia was encountered in one case of the milk-alkali syndrome and in one of acute renal failure. Both patients returned to normal, the first after being put on a low-calcium diet, the second in the diuretic phase.

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