MAGNESIUM METABOLISM IN PRIMARY HYPERPARATHYROIDISM

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SUMMARY

1. Magnesium metabolism has been studied in forty-eight patients with primary hyperparathyroidism. Metabolic balance studies were undertaken in forty-three untreated patients and in fifteen patients after parathyroidectomy. The data obtained are compared with the pattern of magnesium metabolism in healthy adults, as established by analysis of collected nutritional studies. The renal handling of magnesium was assessed from measurements of 24-h renal clearances.

2. The mean serum magnesium in primary hyperparathyroidism was normal but low levels were present in nine of the forty-eight patients. There was a significant inverse correlation between serum levels of calcium and magnesium.

3. The magnesium balance was negative by amounts >5% of the dietary intake in eleven patients, and positive to a similar degree in twenty-one. Patients in negative balance ingested and consequently absorbed less magnesium than those in positive balance; the negative balance was apparently due to inadequate renal conservation of magnesium in the face of this lower intake and, in some cases, despite a low serum magnesium. When related to the level of dietary intake, intestinal net absorption of magnesium tended to be greater than normal.

4. In eleven of twelve patients studied, the urinary output of magnesium was lower after parathyroidectomy irrespective of changes in the serum level of magnesium. This fall in output appeared to depend mainly on reduction in the serum calcium. In untreated patients without advanced secondary renal disease there was a positive correlation between the serum calcium and the clearance ratio CMg/Ccreatinine. Additional mechanisms may contribute to renal loss of magnesium when renal failure is advanced.

5. The tendency to develop a negative magnesium balance and hypomagnesaemia in untreated patients of this series thus appeared related to the height of the serum calcium, the presence of advanced secondary renal disease and inadequate dietary intake.

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6. Significant and sustained hypomagnesaemia after parathyroidectomy occurred only in patients with generalized bone disease. Its development appeared to depend on the inadequacy of the ordinary diet to meet the combined requirements for magnesium of new soft tissue formation and deposition in mineralizing bone.

It is estimated that the skeleton contains 66% of the whole body magnesium of adult man (Widdowson & Dickerson, 1964) and magnesium must be mobilized with calcium and phosphorus when the parathyroid hormone induces removal of bone. In certain animal species, it has also been demonstrated that the parathyroid glands vary their rate of hormonal secretion in response to change in the concentration of magnesium in the blood plasma perfusing them (Care, Sherwood & Potts, 1966; Potts, Buckle, Sherwood, Ramberg, Mayer, Kronfield, Deftos, Care & Aurbach, 1968). In spite of this interrelationship between magnesium and the parathyroid glands, it is uncertain whether the latter are directly concerned with the regulation of magnesium homeostasis; or whether the effects on magnesium are incidental to a primary action on calcium metabolism (Walser, 1967).

A negative magnesium balance in primary hyperparathyroidism was first noted by Bulger & Gausmann (1933) and was described subsequently by Barnes, Krane & Cope (1957a) and Hanna, North, MacIntyre & Fraser (1961). On the basis of these studies and occasional reports of a low serum magnesium in untreated patients, it is sometimes implied that a negative magnesium balance and hypomagnesaemia are common in this disease (Geschwind, 1961; Wacker & Parisi, 1968). Conversely, Basset & Van Alstine (1935), Tibbets & Aub (1937a and b) and Heaton & Pyrah (1963) found the external magnesium balance to be at equilibrium or positive in ten of twelve patients studied by them; the serum magnesium was normal in all of sixteen patients observed by Heaton & Pyrah. The available metabolic data are insufficient to assess the part played by inadequate intake in determining a negative balance.

When present, the negative magnesium balance has usually been attributed to urinary loss of magnesium. All observers agree that parathyroidectomy is followed by a fall in the urinary output of magnesium that may be sufficient to render positive a previously negative external balance; but the mechanisms responsible have not been elucidated. Micropuncture studies in the dog indicate that up to 60% of the magnesium filtered at the glomerulus is reabsorbed in the proximal tubule, probably by a passive process, and that more complete reabsorption occurs at a more distal site in the tubule (Brunette, Wen, Evanson & Dirks, 1969). Under conditions of intravenous loading with magnesium salts, the urinary excretion is determined by glomerular filtration and tubular reabsorption; there appears to be a tubular reabsorptive maximum (Tm) which is increased by parathyroid hormone and reduced by elevation of the serum calcium (Massry, Coburn & Kleeman, 1969). Thus, in primary hyperparathyroidism, several different factors may operate that are potentially capable of increasing or diminishing the renal excretion of magnesium.

The present report is concerned with observations on forty-eight patients with primary hyperparathyroidism, most of whom were studied by metabolic balance. Renal mechanisms were assessed by the calculation of 24-h renal clearances.

**MATERIALS AND METHODS**

Metabolic balance studies were undertaken in forty-three untreated patients with primary hyperparathyroidism and repeated in thirteen of them following parathyroidectomy. In two
additional patients with acute hyperparathyroid crisis, quantitative metabolic observations were limited to the post-operative period. A summary of the calcium metabolism of these patients has been reported (Stanbury, 1968); full details and relevant clinical data will be published elsewhere (Stanbury).

The presence of hyperparathyroid bone disease was assessed by radiographic appearances, the presence of a raised serum alkaline phosphatase and in some patients by bone biopsy.

The general conduct of the balance and the methods of determining calcium, phosphorus and nitrogen were as described previously (Stanbury & Lumb, 1962). Magnesium in serum, urine, dietary and faecal ash was measured by atomic absorption spectrophotometry (Dawson & Heaton, 1961). Except for one post-operative study lasting only 8 days, all metabolic data were based on collections of at least 12–16 days duration; in thirty individual periods of study, assessment of the state of magnesium metabolism was based on collections of 20–44 days. Because of the duration of these metabolic studies, deviations of magnesium balance from equilibrium were considered probably significant when they exceeded ±5% of the magnesium intake. When the external nitrogen balance was positive, it has been assumed that this entailed an obligatory retention of 0.63 mEq (7.6 mg) of magnesium in soft tissue for each 1g of nitrogen retained (Baldwin, Robinson, Zierler & Lilienthal, 1952; Barnes, Gordon & Cope, 1957b).

The renal handling of magnesium in these patients was assessed by deriving an apparent renal clearance from measurements of the rate of magnesium excretion and the serum concentration of total magnesium. In most instances, urinary output was measured over a 24-h period and a single blood sample was obtained in the post-absorptive state. Each reported value was usually the mean of several such determinations, as always were the cited concentrations of serum magnesium and calcium. Since no measurements were made of the serum ultrafiltrable or ionic magnesium, the derived 'magnesium clearance' is a minimum estimate of the true renal clearance; to emphasize this point, it is referred to in the text as CMg or the 'minimal magnesium clearance'. Comparisons made between values of CMg or of the ratio CMg/Ccreatinine in different groups of patients depend on the assumption that the ultrafiltrable fraction is a constant proportion of the serum total magnesium (see Fig. 7).

For comparison with the present findings in primary hyperparathyroidism, especially in respect of the intestinal net absorption of magnesium, it was necessary to establish the statistical pattern of magnesium metabolism in the healthy adult. Data for this purpose were derived largely from the massive compilation of Seelig (1964), excluding studies in which the magnesium intake exceeded 500 mg/day and metabolic periods that followed immediately after one of high magnesium intake. This was supplemented by measurements in thirty-six additional subjects taken from the publications of Jones, Monalo & Flink (1967), Briscoe & Ragan (1966) and Clarkson, McDonald, de Wardener & Warren (1965). The total material used for analysis comprised 332 metabolic balance periods in 186 individuals. Statistical methods were as described by Bailey (1964).

RESULTS

Serum magnesium

The mean concentration of serum magnesium in twenty normal individuals was 1.99 mg/100 ml (SD, 0.16) with a normal range (m ± 1.96 SD) of 1.68–2.30 mg/100 ml. This is in good
agreement with the normal values (m, 2.00 mg/100 ml; range, 1.72–2.28 mg/100 ml) obtained in 176 subjects by Heaton & Pyrah (1963), also using atomic absorption spectrophotometry.

In forty-eight untreated patients with primary hyperparathyroidism, the mean serum magnesium of 1.90 mg/100 ml (SD, 0.31) was not significantly different from that of the normal subjects. The serum magnesium was below normal in nine of the forty-eight patients (Table 1).

The concentration of serum calcium was raised (m, 12.95, SD, 2.4 mg/100 ml) in all but one patient (case 22) who had severe renal failure. There was a significant inverse correlation between the serum concentrations of calcium and magnesium in untreated patients (r = −0.57; n = 48; P < 0.001; y = 2.81 −0.07x; see Fig. 1).

A transitory fall in the concentration of serum magnesium occurs commonly on the day following any surgical operation, the original value usually being restored by the second or third post-operative day (Heaton, 1964). In order to assess the specific effect of parathyroidectomy, post-operative values have been taken as the mean of determinations made between the third and fifteenth day after operation. Excluding patients who had received oral supplements of magnesium salts, appropriate measurements were available from twenty-seven patients. In these patients the mean serum magnesium was 1.86 mg/100 ml (SD, 0.30) before operation and 1.65 mg/100 ml (SD 0.31) after parathyroidectomy. This fall was significant (P < 0.01) but further analysis indicated that it was almost entirely attributable to a group of patients with bone disease (Fig. 2). In fifteen patients without evident bone disease the mean serum magnesium concentration before (m, 1.95, SD, 0.17 mg/100 ml) and after parathyroidectomy (m, 1.84, SD, 0.20 mg/100 ml) was not significantly different (0.05 < P < 0.1).
**TABLE 1. Patients with low serum magnesium before parathyroidectomy**

<table>
<thead>
<tr>
<th>Case</th>
<th>Serum magnesium (mg/100 ml)</th>
<th>Serum calcium (mg/100 ml)</th>
<th>Dietary magnesium (mg/day)</th>
<th>Urinary magnesium (mg/day)</th>
<th>Balance magnesium (mg/day)</th>
<th>Creatinine clearance (ml/min)</th>
<th>$100 \times \frac{CMg}{Ccr}$</th>
<th>Bone disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>1.49 (1.24)</td>
<td>15.2</td>
<td>200</td>
<td>91 (7.6)</td>
<td>+41</td>
<td>*</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>1.31 (1.09)</td>
<td>16.1</td>
<td>218</td>
<td>64 (5.3)</td>
<td>+68</td>
<td>56</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>1.45 (1.21)</td>
<td>18.5</td>
<td>158</td>
<td>60 (5.0)</td>
<td>-23</td>
<td>11</td>
<td>25.4</td>
<td>+</td>
</tr>
<tr>
<td>21</td>
<td>1.65 (1.37)</td>
<td>15.3</td>
<td>131</td>
<td>59 (4.9)</td>
<td>-13</td>
<td>33</td>
<td>7.3</td>
<td>—</td>
</tr>
<tr>
<td>22</td>
<td>1.15 (0.96)</td>
<td>9.5</td>
<td>92</td>
<td>38 (3.2)</td>
<td>-7</td>
<td>10**</td>
<td>20.9</td>
<td>+</td>
</tr>
<tr>
<td>24</td>
<td>1.53 (1.27)</td>
<td>12.5</td>
<td>161</td>
<td>32 (2.7)</td>
<td>+72</td>
<td>20</td>
<td>7.2</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>1.50 (1.25)</td>
<td>19.2</td>
<td>92</td>
<td></td>
<td></td>
<td>9.2</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>0.97 (0.81)</td>
<td>22.7</td>
<td></td>
<td></td>
<td></td>
<td>11</td>
<td>—</td>
<td>+</td>
</tr>
<tr>
<td>23</td>
<td>1.09 (0.91)</td>
<td>12.7</td>
<td></td>
<td></td>
<td></td>
<td>15**</td>
<td>—</td>
<td>+</td>
</tr>
</tbody>
</table>

* Clearance not available; serum creatinine, 1.0 mg/100 ml
** After correction of sodium deficiency.
FIG. 2. The changes in serum level of calcium and magnesium following parathyroidectomy in patients with and without evident bone disease (see text).

Among the patients with bone disease, those with advanced secondary renal disease are indicated by solid lines, the others by interrupted lines. One patient without apparent bone disease is indicated separately by an interrupted line; she had chronic pancreatitis and steatorrhoea and could also have had undetected bone disease.
changes induced by parathyroidectomy in these patients (Fig. 2) appeared indistinguishable from the non-specific effects of surgery described by Heaton (1964). The mean pre-operative serum magnesium in the twelve patients with bone disease (m, 1.76, SD 0.39 mg/100 ml) was lower than in those without bone disease but not significantly so (P<0.1); the post-operative mean value (m, 1.43, SD, 0.28 mg/100 ml) indicated that parathyroidectomy in these patients had produced a highly significant effect on the serum magnesium (P<0.0005). In several patients with bone disease the serum magnesium fell to subnormal levels and the hypomagnesaemia was still present 2–3 weeks after the operation; it was generally associated with hypocalcaemia (Fig. 2).

![Graph](image)

**Fig. 3.** The relationship between the dietary intake and faecal output of magnesium in healthy individuals; data collected from published nutritional studies. The regression line and 95% confidence limits are inserted.

**Faecal magnesium**

It has been suggested that the extreme variability in the relationship between the absolute amount of magnesium ingested and the faecal magnesium can be reduced by expressing the faecal output as a percentage of intake (Heaton & Pyrah, 1963). In the present cases of primary hyperparathyroidism there was an inverse correlation between the absolute intake of magnesium (in mg/day) and the percentile fraction of the intake excreted in the faeces (r = -0.355; 0.01 < P < 0.02; n = 46; y = 68.7% - 0.08x). A similar trend, although not statistically significant, is evident in the collected data from previously published studies of primary hyperparathyroidism and we consider this method of comparison to be invalid.
There was a close positive correlation between the dietary intake and faecal output of magnesium in the patients with hyperparathyroidism ($r = +0.635$, $P<0.001$, $n = 46$), with the regression equation $y = 0.33x + 38$ mg/day (Fig. 4). The corresponding regression for the collected normal control data (332 collection periods) was $y = 0.599x + 5.2$ mg/day (Fig. 3), $r = +0.76$, $P<0.001$. Virtually all the data for hyperparathyroidism were within the very wide confidence limits of the normal but they were not distributed symmetrically about the normal regression (Fig. 4). The data from seven of the present cases of hyperparathyroidism fell above this regression line and thirty-six below it. Of similar data from seventeen published studies in primary hyperparathyroidism, two fell above the normal regression and twelve below (Fig. 4). This suggests that the faecal magnesium tends to be less than normal in this disease. The data from the small number of present patients with advanced secondary renal disease ($C_{\text{creatinine}} < 25$ ml/min) were not distributed differently from the remainder (Fig. 4); renal failure appeared not to impair magnesium absorption.

In eleven out of twelve patients, studied before and after parathyroidectomy when ingesting the same amount of magnesium (Table 2), the faecal magnesium increased by 6-4 to 86-9% ($\bar{m}$, 31%) after the operation. In spite of this evidence of effect in the individual patient, the mean faecal magnesium for the group of eleven patients before operation ($\bar{m}$, 91-6, SD, 25-7

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**Fig. 4.** The relationship between the dietary intake and faecal output of magnesium in patients with primary hyperparathyroidism. The heavy line is the regression calculated for forty-six personal cases (●); the open circles (○) refer to cases with $C_{\text{creatinine}} < 25$ ml/min. The squares (□) indicate data obtained from previously published metabolic studies cited in the text: these data were not incorporated in the regression analysis.
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mg/day) was not significantly different from that after operation (mean, 116.7, SD, 26.5 mg/day).

Six patients with untreated primary hyperparathyroidism received supplementary oral therapy with calcium in the form of the glucogalactoheptonate (Table 3). In one patient with osteitis fibrosa and osteomalacia (case 16), who retained massive amounts of calcium, magnesium absorption also increased. In the other five, the faecal magnesium increased by amounts equivalent to 1.6 to 17% of the dietary intake (Table 3). Although this effect was small, it was sufficient to produce a significant change in the external balance of magnesium when the intake of this ion was low (case 20, Table 3). The ratio between the molar increment in calcium net absorption and decrement in magnesium net absorption varied widely between 3:3:1 and 60:1. These data support the contention of Walser (1967) that the effects of calcium on magnesium absorption are non-specific, rather than produced by competition for a common transport mechanism.

**Magnesium balance**

Assuming an error in prolonged balance studies of ±5%, the external magnesium balance was negative in eleven patients and positive in twenty-one, there being eleven patients

<table>
<thead>
<tr>
<th>Dietary intake</th>
<th>Net absorption</th>
<th>Urinary output</th>
<th>$100\times CM_{\alpha}/C_{\alpha}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>+VE</td>
<td>+VE</td>
<td>+VE</td>
<td></td>
</tr>
<tr>
<td>-VE</td>
<td>-VE</td>
<td>-VE</td>
<td></td>
</tr>
<tr>
<td>368</td>
<td>244</td>
<td>25.4</td>
<td></td>
</tr>
</tbody>
</table>

**FIG. 5.** A comparison of patients with positive or negative magnesium balances exceeding 5% of the dietary intake. Open circles (○) refer to patients with $C_{\text{creatinine}}<35$ ml/min.

Mean | 207.8 | 147.5 | 111.2 | 55.9 | 77.9 | 75.2 | 4.68 | 9.98 
S D  | 53.8  | 35.2  | 41.5  | 20.2 | 39.3 | 20.1 | 2.31 | 7.55 
$P$  | <0.002 | <0.001 | N.S.  | <0.01 |
<table>
<thead>
<tr>
<th>Case duration (days)</th>
<th>Pre-operative balances</th>
<th>Post-operative balances</th>
<th>Serum changes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Magnesium (mg/day)</td>
<td>Faeces (g/day)</td>
<td>Urine (mg/day)</td>
</tr>
<tr>
<td>1</td>
<td>207 (1030)</td>
<td>82 (396)</td>
<td>119 (686)</td>
</tr>
<tr>
<td>2</td>
<td>198 (737)</td>
<td>120 (399)</td>
<td>95 (298)</td>
</tr>
<tr>
<td>3</td>
<td>368 (1164)</td>
<td>124 (620)</td>
<td>190 (435)</td>
</tr>
<tr>
<td>4</td>
<td>167 (466)</td>
<td>91 (424)</td>
<td>72 (421)</td>
</tr>
<tr>
<td>5</td>
<td>177 (1065)</td>
<td>110 (858)</td>
<td>75 (103)</td>
</tr>
<tr>
<td>6</td>
<td>200 (775)</td>
<td>68 (698)</td>
<td>91 (367)</td>
</tr>
<tr>
<td>7</td>
<td>218 (930)</td>
<td>86 (747)</td>
<td>64 (222)</td>
</tr>
<tr>
<td>8</td>
<td>139 (200)</td>
<td>61 (265)</td>
<td>(lost)</td>
</tr>
</tbody>
</table>
The figures in parentheses (x/y) in the first column indicate the duration of metabolic collection in the pre- and post-operative studies respectively. Data for calcium metabolism are included in parentheses immediately beneath the appropriate data for magnesium. 'Changes' in serum magnesium and calcium are the differences between the mean values prevailing during the pre- and post-operative studies. Cases 1−5 and 13 had no clinically evident bone disease. Case 4 was emotionally disturbed during the pre-operative study and her high faecal calcium is atypical (Stanbury, unpublished observation). Cases 6−12, 14 and 15 had generalized bone disease which, in cases 8 and 9, was a combination of osteitis fibrosa and severe osteomalacia (Stanbury, unpublished observation). Cases 10−12, 14 and 15 also had advanced secondary renal disease.
approximate equilibrium. In five patients, the negative balance was between 13 and 35% of the intake; this entailed daily losses of 18–43 mg. In thirteen patients the positive balance was equivalent to 12 to 51.5% of intake with a daily retention of 20–111 mg.

Fig. 5 shows data from all patients in whom the positive or negative balance exceeded 5% of the dietary intake. The dietary intake of magnesium was much higher in the patients with a positive balance and their mean daily net absorption was double that of the patients in negative balance. The mean urinary output of magnesium was the same in the two groups (Fig. 5). This implies that the negative balance was attributable to inadequate renal conservation of magnesium in the face of a lower intake. Despite their lower dietary intake, the patients in negative balance excreted the equivalent of 51.8% (SD 12%) of the intake in the urine; those in positive balance excreted 36.2% (SD 12%). The excreted fraction of filtered magnesium (\(CMg/C_{\text{creatinine}}\), Fig. 5) was significantly higher in the group with negative balance; six of the eleven patients in this group had advanced renal impairment (\(C_{\text{creatinine}} < 35\) ml/min). The serum magnesium was not significantly different in the two groups (positive balance, \(\bar{m}, 1.96\), SD 0.19 mg/100 ml; negative balance, \(\bar{m}, 1.87\), SD 0.34 mg/100 ml; \(P > 0.1\)), so that renal wasting of magnesium was not attributable to a higher serum level in the patients with negative balance. The mean serum calcium in those with negative magnesium balance (\(\bar{m}, 13.38\), SD 2.58 mg/100 ml) was higher than in the group with positive balance (\(\bar{m}, 12.27\), SD 1.53 mg/100 ml) but not significantly so.

### TABLE 3. The effect of ingested calcium on the faecal magnesium

<table>
<thead>
<tr>
<th>Case</th>
<th>Supplementary calcium (g/day)</th>
<th>Duration therapy (days)</th>
<th>(\Delta) Calcium net absorption (mg/day) (mEq/day)</th>
<th>(\Delta) Faecal magnesium (mg/day) (mEq/day)</th>
<th>(\Delta) Balance magnesium (mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>1.14</td>
<td>16</td>
<td>+453 (22.6)</td>
<td>+26 (2.16)</td>
<td>-21</td>
</tr>
<tr>
<td>16</td>
<td>1.52</td>
<td>36</td>
<td>+1314 (65.7)</td>
<td>-13 (1.10)</td>
<td>+7</td>
</tr>
<tr>
<td>17</td>
<td>1.14</td>
<td>24</td>
<td>+301 (15.0)</td>
<td>+6 (0.50)</td>
<td>-4</td>
</tr>
<tr>
<td>18</td>
<td>0.76</td>
<td>32</td>
<td>+165 (8.25)</td>
<td>+21 (1.74)</td>
<td>-6</td>
</tr>
<tr>
<td>19</td>
<td>0.76</td>
<td>12</td>
<td>-38 (1.90)</td>
<td>+3 (0.24)</td>
<td>-6</td>
</tr>
<tr>
<td>20</td>
<td>0.76</td>
<td>20</td>
<td>+64 (3.20)</td>
<td>+15 (1.24)</td>
<td>-12</td>
</tr>
<tr>
<td>20</td>
<td>1.52</td>
<td>20</td>
<td>+120 (6.0)</td>
<td>+22 (1.82)</td>
<td>-21</td>
</tr>
</tbody>
</table>

Post-operative metabolic balance studies in cases 13 to 15 (Table 2) were especially instructive. Case 14 had bone disease, severe hypercalcaemia (19.2 mg/100 ml), a slightly subnormal serum magnesium (1.5 mg/100 ml) and irreversible renal failure (\(C_{\text{creatinine}} < 9.5\) ml/min). Intravenous magnesium sulphate (84 mEq or 1.01 g of Mg) restored a normal serum magnesium, which was maintained during the next month. Presumably because of the renal failure, there was no retention of calcium during this post-operative period (Table 2); the small retention of magnesium was accountable by protein anabolism. Case 15 (body weight, 35 kg) presented with severe bone disease, renal failure (\(C_{\text{creatinine}} < 11\) ml/min), hypomagnesaemia (0.97 mg/100 ml) and hypercalcaemic crisis (serum calcium 20–27 mg/100 ml). She received 252 mEq (3.02 g) of magnesium intravenously, during and immediately following parathyroidectomy. Despite this, the mean serum magnesium between the third and seventh post-operative weeks
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was 1.49 mg/100 ml. During this period the daily retention of magnesium was 34 mg, of which about half was accountable by nitrogen retention (Table 2); the ratio by weight of calcium to magnesium presumably deposited in bone was approximately 2.5:1. As renal function improved progressively during the following month, intestinal absorption of calcium increased and the daily retention of calcium was 0.4 g (Table 2). There was no incremental retention of magnesium, implying a Ca:Mg deposition in bone of 30:1. In case 13 (Table 2), who received supplementary magnesium during post-operative metabolic studies, the ratio of calcium to magnesium retention was 1.6:1. These results suggest that the amount of magnesium deposited in bone after parathyroidectomy reflects passively the availability of the ion. If a low Ca:Mg ratio in newly forming bone confers any benefit or subserves any physiological function, a normal diet may not provide sufficient magnesium to establish this ratio.

Fig. 6. The relationship of the daily urinary output of magnesium to the dietary intake (above) and to the daily intestinal net absorption of magnesium (below).
The urinary excretion of magnesium

With the exception of one patient, who excreted only 13 mg/day, the daily urinary excretion of magnesium was within the normal range but the mean output (81, SD 32 mg/day) was lower than in healthy individuals receiving their customary diet (Heaton & Pyrah, 1963; Evans & Watson, 1966). The apparent renal clearance of magnesium (CMg) varied between the extreme of 0·4 and 6·4 ml/min (m, 2·75, SD 0·92 ml/min).

The relation to the dietary intake and intestinal net absorption of magnesium

There was a close correlation between the daily urinary output of magnesium and both the dietary intake ($r = +0·66, P<0·001$) and the daily intestinal net absorption of magnesium ($r = +0·68, P<0·001$; see Fig. 6). This suggests that the main determinant of urinary output was the amount absorbed from the diet; or that intestinal absorption was geared to the rate of renal excretion. There was no significant correlation between the clearance ratio $\text{CMg}/C_{\text{creatinine}}$ and the intestinal net absorption of magnesium ($r = +0·28, n = 34, P>0·1$; excluding eight cases with advanced renal impairment, see below). Thus, the variation in urinary output with change of net absorption appeared not to be associated with altered renal tubular handling of magnesium.

When urinary output was expressed as a percentage of intake (Heaton & Pyrah, 1963), there was no correlation between the two ($r = -0·1, n = 43; y = 46·4%-0·025x$).

The relation to the serum level of magnesium and to the creatinine clearance

There was no significant correlation between the serum level and urinary output of magnesium ($r = +0·27, n = 42, 0·05<P<0·1$). In five patients with low levels of serum magnesium, between 1·15 and 1·53 mg/100 ml (0·96 to 1·28 mEq/l), the urinary output was between 32 and 91 mg/day (Table 1).

The creatinine clearance was correlated with the minimal renal clearance of magnesium (CMg) ($r = +0·50, n = 42, P<0·001$) and with the daily urinary output of magnesium ($r = +0·58, n = 42, P<0·001$). The daily urinary output of magnesium was also correlated with the 'rate of magnesium filtration', as crudely estimated by the product $C_{\text{creatinine}} \times \text{serum total Mg}$ ($r = +0·495, n = 42, P<0·001$). There was, however, a highly significant correlation between the creatinine clearance and the magnesium content of the diet ($r = +0·63, P<0·001$). The partial correlation between urinary magnesium and creatinine clearance, with the effect of diet eliminated, was not significant ($r = +0·28, 0·05<P<0·1$). The partial correlation between the dietary and urinary magnesium remained significant when the influence of creatinine clearance was excluded ($r = +0·47, 0·001<P<0·01$).

Fig. 7 shows the relationship between the creatinine clearance and the clearance ratio, $\text{CMg}/C_{\text{creatinine}}$, in (a) forty-two of the present cases of hyperparathyroidism and (b) forty cases of primary renal disease with creatinine clearance between 8 and 100 ml/min (constructed from published data of Better, Kleeman, Gonick, Varrady & Maxwell, 1967 and Popovtzer, Massry, Coburn & Kleeman, 1969). In both groups of cases the clearance ratio increased with the degree of renal impairment, the increase becoming asymptotic when the creatinine clearance fell below 20–30 ml/min. This is illustrated by the separately calculated regressions for cases with creatinine clearance $>30$ ml/min and $<25$ ml/min (Fig. 7). Thus, when the primary hyperparathyroidism was complicated by advanced secondary renal disease, the fraction of
filtered magnesium that was excreted appeared to be primarily a function of the rate of glomerular filtration.

FIG. 7. The effect of progressive impairment of renal function on the renal tubular handling of magnesium; a comparison of primary hyperparathyroidism with primary renal disease.

(a) In the present cases of primary hyperparathyroidism (O, ordinate at the left) the magnesium to creatinine clearance ratio was derived using $CMg$, the minimal magnesium clearance as described in Methods.

(b) In the cases of primary renal disease (●, ordinate on the right), the clearance ratio was derived using the renal clearance of diffusible magnesium. Assuming the diffusible fraction to be statistically 75% of the total serum magnesium (Better et al., 1967), the ordinate on the right has been factorized accordingly to bring the two sets of data into alignment.

(c) The curve (from Steele et al., 1968) also relates to primary renal disease; it was derived using $CMg$ as an index of magnesium clearance and inulin clearance as a measure of glomerular filtration rate (ordinate at the left).

(d) Separate regressions are inserted for cases of primary hyperparathyroidism with $C_{\text{creatinine}} > 30$ ml/min (B) and < 25 ml/min (A).
Fig. 8. The relationship of the renal excretion of magnesium to the abnormalities of calcium metabolism in primary hyperparathyroidism. The open circles (○) relate to cases with $C_{\text{creatinine}} < 25 \text{ ml/min}$. The correlations demonstrated in (a), (b) and (c) were all significant in the mathematical sense; but only the relationship shown in (c) could be dissociated from the coincidental effects of differences in the amount of magnesium ingested (see text).

The regression shown in (b) is effectively identical with the regression derived by Sutton & Watson (1969) for twenty females with primary hyperparathyroidism and renal calculi ($y = 0.073x + 62.5$); it is similarly different from the relationship demonstrated by these authors in 120 control subjects.
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The relation to the abnormal calcium metabolism

There was a positive correlation between the daily urinary output of magnesium and that of calcium \((r = +0.47, n = 43, 0.001 < P < 0.01)\); and there was a closer correlation between the estimate of 'glomerular filtered calcium' \((C_{\text{creatinine}} \times \text{serum total Ca})\) and the urinary output of magnesium \((r = +0.58, P < 0.001, \text{see Fig. 8})\).

This suggested that the urinary excretion of magnesium was influenced by the severity of the hyperparathyroidism; but, because of the demonstrated correlation between \(C_{\text{creatinine}}\) and the dietary magnesium (see above), it was necessary to eliminate the contribution of \(C_{\text{creatinine}}\) in the above derived relationships with calcium. There was no correlation between the serum calcium itself and the urinary output of magnesium \((r = +0.09)\); and the correlation between the serum calcium and the daily urinary output of calcium was not close \((r = +0.33, n = 44, 0.01 < P < 0.05)\). Conversely, the correlation between the 'filtered load of calcium' \((C_{\text{creatinine}} \times \text{serum total Ca})\) and the urinary calcium was highly significant \((r = +0.76, n = 44, P < 0.001)\).

Thus, the factor, \(C_{\text{creatinine}}\), is critically involved in determining the correlations observed between the urinary magnesium and the two parameters of calcium metabolism. In consequence, the effects of hypercalcaemia or hypercalciuria cannot be dissociated with certainty from the coincidental effect of different magnesium intakes.

It has been demonstrated experimentally that the renal tubular reabsorption of magnesium is reduced when the serum calcium, and thus the concentration of calcium in the glomerular filtrate, is acutely increased (Coburn, Massry, Chapman & Kleeman, 1967; Massry et al, 1969; Popovtzer et al, 1969). Consequently the relationship was explored between the serum calcium and the clearance ratio \(CMg/C_{\text{creatinine}}\) (Fig. 8C), excluding the eight cases with \(C_{\text{creatinine}} < 25\) ml/min (see above). These variables were significantly correlated \((r = +0.45, n = 34, P < 0.01)\) and there was no correlation between serum Ca and \(C_{\text{creatinine}}\) \((r = +0.03)\). When the influence of \(C_{\text{creatinine}}\) on \(CMg/C_{\text{creatinine}}\) \((r = -0.42, \text{see Fig. 7})\) was eliminated, the partial correlation coefficient between serum Ca and \(CMg/C_{\text{creatinine}}\) was +0.51 \((P = 0.001)\).

Thus, the fraction of filtered magnesium that is excreted apparently increases with elevation of the serum calcium.

The effect of parathyroidectomy

In ten of eleven patients studied before and after the operation (Table 2), parathyroidectomy reduced the urinary excretion of magnesium by amounts between 10 and 48 mg/day \((\text{m}, 30\) mg/day). In seven of these patients, the fall in urinary output occurred without significant change in the serum magnesium \((\Lambda, -0.15 \text{ to } +0.20 \text{ mg/100 ml, Table 2})\); in the other three, the mean serum magnesium after parathyroidectomy was 0.3 to 0.5 mg/100 ml lower than the mean values before operation. The largest decrements in urinary magnesium occurred in association either with a massive fall in the serum calcium alone (cases 7, 10, Table 2) or with a significant reduction of the serum magnesium accompanied by a more modest fall of the serum calcium (cases 9, 11, 12).

DISCUSSION

A low serum magnesium has been reported in untreated primary hyperparathyroidism by Harmon (1956), Agna and Goldsmith (1958) and Hanna et al. (1961) but it is exceptional. It was found in nine of the present forty-eight cases, and the inverse correlation between the
serum levels of magnesium and calcium (Fig. 1) suggests that those with the most severe hyperparathyroidism tend to have the lowest serum magnesium.

It is not likely that faecal loss of magnesium contributed significantly to the development of hypomagnesaemia. In the present patients (Table 2) and in other published studies (Heaton & Pyrah, 1963), the faecal magnesium increased following parathyroidectomy. Although it was reported by Greenwald & Cross (1925) that continued administration of parathyroid extract caused an increased faecal output of magnesium in the dog, their results were few and inconsistent and comparable observations appear not to have been made subsequently. In the present collection of data from healthy subjects, the regression of faecal magnesium on dietary intake (Fig. 3) leads one to expect that the faecal output would become very small as the intake was reduced towards zero. This expectation has been realized by direct observation; in subjects ingesting 6–10 mg of magnesium per day, the faecal output invariably fell to less than 12 mg/day (Barnes, Cope & Harrison, 1958; Shils, 1969). The analogous regression in the cases of hyperparathyroidism (Fig. 4) had a lesser slope and a greater intercept at zero intake; the difference between the regression coefficients of the healthy and the hyperparathyroid subjects was significant at less than the 1% level \((d = 3.93; P < 0.001)\). This could mean that the faecal magnesium in primary hyperparathyroidism may be greater than normal when the dietary intake is low and that net intestinal absorption is greater than normal at higher levels of intake. There were, however, relatively few observations at low levels of magnesium intake (< 150 mg/day) in either group and this possibility cannot be accepted without further study. There were also too few patients with advanced secondary renal disease to warrant separate statistical treatment; in agreement with the findings of Clarkson et al. (1965) and in contradiction to what is found in respect of calcium (Stanbury & Lumb, 1962), there was no suggestion that renal failure was associated with impaired intestinal absorption of magnesium.

The probable cause of hypomagnesaemia in primary hyperparathyroidism is loss of magnesium in the urine. In healthy individuals ingesting a diet containing 1 mEq of magnesium, the serum magnesium fell to 1.22 ± 0.18 mEq/l, and the daily urinary output to 1.01 ± 0.21 mEq/day within a period of 6 days (Gitelman, Graham & Welt, 1966); with more prolonged deprivation of magnesium, the urinary output fell to still lower levels (Barnes et al., 1958; Shils, 1969). In four of the present patients (cases 6, 7, 10, 22; Table 1) with serum magnesium between 0.96 and 1.24 mEq/l, the urinary output was between 3.2 and 7.6 mEq/day. There thus appeared to be an impaired renal conservation of magnesium, in the sense that the urinary output was inappropriately high for the prevailing serum level. Even although the urinary excretion of magnesium fell following parathyroidectomy (Table 2; Heaton & Pyrah, 1963), urinary wasting of magnesium before the operation cannot be attributed to the direct action on the kidney of an excess of circulating parathyroid hormone. Evidence from experiments in animals indicates that parathyroid hormone increases the renal tubular reabsorption of magnesium (Massry et al., 1969); and, in acute experiments, administration of parathyroid extract has reduced the urinary output of magnesium in man (Gill, Bell & Bartter, 1967; Shelp, Steele & Rieselbach, 1969). Administration of parathyroid extract has also been shown to cause a slight rise in the serum magnesium in animals (Greenberg & Mackey, 1932; Cheek & Teng, 1960; Wallach, Bellavia & Schorr, 1966) and man (Gill et al., 1967; Zimmett & King, unpublished observations). Its more prolonged administration has apparently caused an increased urinary excretion of magnesium in man (Bulger & Gaussman, 1933; Tibbetts & Aub, 1937b; Gill et al., 1967). While the latter effect would tend to deplete body stores of magnesium,
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it appears from the present study and others (Heaton & Pyrah, 1963; Bassett & Van Alstine, 1935) that the urinary losses are usually offset by intestinal absorption. In view of this, and the tendency for the action of parathyroid hormone on bone and kidney to sustain or elevate the serum magnesium, it is necessary to seek alternative explanations for the exceptional case with hypomagnesaemia.

The present data suggest that the urinary output of magnesium in primary hyperparathyroidism is chiefly dependent on two factors; (a) the amount of magnesium ingested with the diet and (b) the effect of hypercalcaemia on the renal tubular reabsorption of magnesium. The statistical treatment suggests that the latter effect is proportionate to the degree of hypercalcaemia (Fig. 8c) and, if the dietary intake is low, there may be insufficient magnesium available for intestinal absorption to permit the compensation of urinary losses (Fig. 5; Table 2). With progression of secondary renal disease, the obligatory increase in the fractional excretion of filtered magnesium (Fig. 7) may also contribute to urinary wasting of magnesium. There was an advanced degree of secondary renal impairment in seven of our nine patients with hypomagnesaemia and, when measured, the ratio $CMg/C_{\text{Creatinine}}$ was high despite the low concentration of serum magnesium (Table 1). The relative contribution of these various factors to the urinary output of magnesium in different patients is illustrated by comparing the pre- and post-operative metabolic balances in Table 2. In case 10 (see also Table 1) the massive post-operative fall in the serum concentration of calcium was associated with a 68% (42 mg/day) reduction in the urinary output of magnesium; this was sufficient to establish a positive balance of magnesium, despite the low intake of 158 mg/day. Parathyroidectomy in case 12 (Table 2) produced a fall in the serum concentration of both calcium and magnesium, and the urinary excretion of magnesium was reduced by 31 mg/day; the urinary output after operation (55 mg/day) was still equivalent to almost 50% of the dietary intake and the negative external balance was uninfluenced. Since defective renal conservation of magnesium was still apparent after correction of the hyperparathyroidism, an intrinsic renal defect must have contributed to urinary wasting of magnesium in this patient. In cases 12, 22 and 23 (Tables 1 and 2), the secondary renal lesion was associated with sodium wasting and each patient had required treatment with saline infusions and supplementary oral salt before metabolic studies were started. Since the renal clearances of sodium and magnesium are closely correlated under conditions of sodium loading (Massry et al., 1967, 1969), this procedure could have occasioned further renal loss of magnesium. This renal salt wasting and its treatment may explain the aberrant position of cases 22 and 23 in Fig. 1. It is to be emphasized, however, that hypomagnesaemia is not always associated with a concomitant negative external balance of magnesium (Table 1); conversely, a negative balance is compatible with a normal or raised serum concentration of magnesium. In a group of patients with primary renal disease and $C_{\text{Creatinine}} < 7.5$ ml/min studied by Lim, Dong & Khoo (1969) hypermagnesaemia was associated with a mean 23.5% reduction in muscle magnesium. When the rate of glomerular filtration falls below about 10 ml/min in patients with primary renal disease, the kidneys may be unable to excrete absorbed dietary magnesium without elevation of the serum concentration of magnesium (Steele, Wen, Evenson & Reiselbach, 1968). Since hypomagnesaemia in primary hyperparathyroidism tends to occur in patients with secondary renal disease (Table 1: Sutton, 1970), the renal wasting of magnesium in this disease may protect against the development of hypermagnesaemia as renal failure advances. The metabolic data acquired in the present study suggest that a negative magnesium balance can be countered by an adequate oral intake of
magnesium; but it is questionable whether a deliberate attempt should be made to correct asymptomatic hypomagnesaemia before parathyroidectomy. Magnesium deficiency appears to reduce the rate of bone catabolism in the rat (MacManus & Heaton, 1969) and to limit the capacity of parathyroid hormone to raise the serum calcium in man (Estep, Shaw, Watlington, Hobe, Holland & Tucker, 1968). Hypothetically these effects of magnesium deficiency could mitigate the effects of the hyperparathyroidism.

In the present series of patients the fall in the concentration of serum magnesium after parathyroidectomy was significant and sustained only in those with bone disease; it was commonly associated with prolonged post-operative hypocalcaemia (Fig. 2). This is in agreement with the previously observed association between post-operative hypomagnesaemia and generalized bone disease (Potts & Roberts, 1958; Hanna et al., 1961; Heaton & Pyrah, 1963). It also suggests that deposition of magnesium in newly forming bone could be the principal cause of the reduced serum magnesium after parathyroidectomy. Parathyroidectomy is also generally followed by increased assimilation of nitrogen (Stanbury, unpublished observation; see also Table 2) and this formation of protein must be associated with incorporation of magnesium into soft tissue. If it is assumed that the newly formed tissue has the same Mg:N ratio as muscle (see Methods), it is possible to estimate the approximate apportionment between soft tissues and bone of the magnesium retained after parathyroidectomy. Six of the present patients studied after parathyroidectomy were in positive balance for both calcium and magnesium (Table 2). In three without bone disease (cases 1, 3, 4), virtually all the small amount of magnesium retained was accountable in terms of protein anabolism. Even in patients with bone disease, the greater fraction of retained magnesium (case 6, 86%; case 9, 77%; case 15, 54%) was similarly accountable; only in case 7 was the major fraction (82%) apparently deposited in bone. The incorporation of magnesium into newly forming soft tissue is regarded as an intrinsic part of the growth of that tissue (Walser, 1967); deposition of magnesium in bone is probably a passive consequence of bone crystal formation (Neuman & Neuman, 1958). If the combined requirements of protein formation and bone mineralization after parathyroidectomy cannot be met by the magnesium absorbed from the diet, the serum magnesium will fall; this can be prevented by the provision of an appropriate oral supplement of magnesium salts (Hanna et al., 1961).

The present data suggest that there may be a wide variation in the Mg:Ca ratio of the mineral deposited in the bone formed after parathyroidectomy. Factors influencing this ratio include the amount of magnesium absorbed from the diet, the competing demands of protein anabolism in extraskeletal tissues, and the rate of deposition of calcium in the bone. The variable chemical composition of the crystals deposited will tend subsequently to impose corresponding chemical changes on the circumambient extracellular fluid of bone, with which they are in solution equilibrium (Neuman & Neuman, 1958). The formation of crystals of low Mg:Ca ratio could thus entail a low concentration of magnesium in the fluid environment of the osteocytes incorporated into the newly mineralized bone. In a variety of clinical conditions, magnesium deficiency and/or hypomagnesaemia has apparently been responsible for the development of hypocalcaemia (Fletcher, Henly, Sammons & Squire, 1960; Fourman & Morgan, 1962; Heaton & Fourman, 1965; Shils, 1969). Since such hypocalcaemia is unresponsive to the administration of parathyroid hormone (Estep et al., 1968), it seems likely that magnesium deficiency influences the serum concentration of calcium through an effect on bone. It is conceivable that the development of hypocalcaemia, following parathyroidectomy in patients with bone disease (Fig. 2), is related causally to magnesium deficiency in bone.
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