CALCIUM SUPPRESSION AND RENAL PHOSPHORUS THRESHOLD TESTS IN THE DIAGNOSIS OF HYPERPARATHYROIDISM

By

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ABSTRACT

Using a standard infusion of 500 mg of calcium gluconate, and collecting urine in four hourly fractions for 36 hours in patients whose calcium and phosphorus intake had been previously stabilised for 3 days a satisfactory difference in the degree of inhibition of phosphate excretion between hyperparathyroidism, and hypo- and hyperparathyroidism was achieved. The value of the renal phosphorus threshold estimation is diminished by the finding of threshold figures between 2.0 and 3.0 mg/100 ml in both hyperparathyroidism and normal subjects.

The diagnosis hyperparathyroidism still presents many problems unless the disease is in a florid state of activity. With the exception of some recent publications (Pronove & Bartter 1961; Goldsmith et al. 1962; Hyde et al. 1960; Randall & Keating 1958; Riddick & Reiss 1962); most authors (Albright et al. 1934; Albright 1948; Hellström 1954; Hellström & Ivemark 1962; Cope 1960; Black 1961; McGeown & Morrison 1959; McGeown 1961a, b, 1963) depend on the demonstration of a persistent hypercalcaemia before a diagnosis of hyperparathyroidism is made unless there is overt osteitis fibrosa cystica. Demonstration of hypercalcaemia can be delayed if the elevation is borderline or if the plasma calcium is fluctuating (McGeown & Morrison 1959). The results of pathophysiological studies of tubular reabsorption of phosphate demon-

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strated by Chambers et al. (1956), Kyle et al. (1958) and Talpers & Stein (1959) were shown to be unsatisfactory as a diagnostic aid for hyperparathyroidism by Reynolds et al. (1960 a, b) owing to the considerable overlap between controls and abnormal states. The latter workers also demonstrated that the phosphate excretion index (P. E. I.) of Nordin (1958, 1961), Nordin & Fraser (1960), becomes normal if the TrP is within the normal range. Howard's concept (Howard et al. 1952, 1953) of hypercalcaemic inhibition of parathormone secretion reflected by diminution of phosphate excretion has been found satisfactory by Pronove & Bartter (1961) and Kyle et al. (1962). However, Moore & Smith (1963) failed to confirm Pronove's observation.

More recently Hyde et al. (1960) and McSwiney (1961) applying the renal phosphorus threshold estimation procedure of Anderson (1955) to the diagnosis of hyperparathyroidism in renal calculi were enabled to make a diagnosis in the absence of hypercalcaemia. As this procedure can readily be applied to all cases of renal calculi and would clearly be most valuable if satisfactory results were obtained it was decided to evaluate it carefully. We also decided to reinvestigate the value of the calcium suppression test by attempting to improve its accuracy by fully stabilising the calcium and phosphate intake before and during the test and also by the collection of urine at shorter intervals over a longer period of time than hitherto used so that the suppression phase might be more clearly separated from the initial phosphaturic phase and the terminal rebound effect.

MATERIALS AND METHODS

Thirty eight patients and nine normal controls form the basis of this study. Nine patients had hyperparathyroidism, six surgically proven. Two had negative explorations but have persistent hypercalcaemia, steroid resistant. One patient refused operation. Twenty two patients had nephrolithiasis presumed not due to hyperparathyroidism for multiple reasons, e.g. history of unilateral calculi, pyelonephritis or obstruction demonstrated at operation, normocalcaemia, prolonged follow up and negative tests. Seven patients had hypoparathyroidism, six surgical and one idiopathic hyperparathyroidism.

All patients on whom a calcium suppression test was carried out were placed on a diet of 200 mg Ca, 600 mg P for a three day stabilisation period prior to urinary collections and during the 72 hours of the test. Urine was collected in 12 hourly lots for the 36 hours prior to infusion. A standard infusion of 500 mg of calcium gluconate in 0.9% NaCl was then given over 3 hours beginning at 8.00 p.m. and after the beginning of the infusion urine was collected in four-hourly lots for a further 36 hours. The per cent deviation of four hourly phosphate output from the average four hourly output during the first 36 hours was estimated.

Renal phosphorus threshold was estimated by the method of Anderson (1955) as modified by Hyde et al. (1960). All tests were personally supervised by one person. All urine was acidified with HCl; phosphorus was estimated as reduced phosphomolybdate (Fiske & Subbarow 1925).
Table 1.
Effects of 500 mg calcium on phosphate excretion in normal, hyperparathyroidism, hypoparathyroidism and in nephrolithiasis; inhibition exceeds 50% except in cases of hyper- and hypoparathyroidism. No consistent difference either in initial increase in phosphaturia nor in rebound effect was found.

<table>
<thead>
<tr>
<th>Controls subject</th>
<th>Maximum increase in phosphaturia</th>
<th>Maximum inhibition in phosphaturia</th>
<th>©Rebound« increase in phosphaturia</th>
<th>Serum calcium mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. E.</td>
<td>200</td>
<td>92</td>
<td>12-16</td>
<td>46</td>
</tr>
<tr>
<td>A. Y.</td>
<td>20</td>
<td>73</td>
<td>12-16</td>
<td>149</td>
</tr>
<tr>
<td>H. A.</td>
<td>30</td>
<td>62</td>
<td>12-16</td>
<td>10</td>
</tr>
<tr>
<td>B. R.</td>
<td>30</td>
<td>96</td>
<td>16-20</td>
<td>0</td>
</tr>
<tr>
<td>K. E.</td>
<td>12</td>
<td>95</td>
<td>12-16</td>
<td>94</td>
</tr>
<tr>
<td>R. S.</td>
<td>0</td>
<td>58.6</td>
<td>12-16</td>
<td>55</td>
</tr>
</tbody>
</table>

Hyperparathyroidism
Subject  Type
McC. adenoma 0 32 12-16 59 11.5-13.5
F. L. hyperplasia 44 38 12-16 4 11.7
B. hyperplasia 8 36 33 10.7-11.0
L. adenoma 92 39 20-24 16 12.2
McH. adenoma 58 38 20-24 38 10.3
Br. adenoma 0 0 0 15.0
O'B. left hospital – 34 12-16 – 11.6-13.0

Nephrolithiasis
Subject
S. M. (R) hydronephrosis 26 76 20-24 12
F. O. calyceal diverticulum 46 80 12-16 116
O'R. familial calculi 40 72 16-20 0
C. A. (R) pyelonephritis 0 78 10-14 64
K. E. (R) hydronephrosis 0 61 16-20 91
O'C. pyelonephritis 155 56 20-24 51
K. I. no cause found 0 82 12-16 37

Hypoparathyroidism (Surg.)
Subject
McC. 12 20-24
C. A. 28 20-24
McC. 45 12-16
Dw. 25 12-16
O'R. 20 16-20
RESULTS

Calcium Suppression Test

Following calcium infusion the phosphate output followed the pattern previously described by Nordin & Fraser (1954). There is an initial increase in phosphaturia for eight hours, followed by a steady decline until 16 to 20 hours after which there is an increase reaching base-line levels at 28 or 32 hours (see Fig. 1). The maximum initial increase, inhibition and «rebound» increase for each case, expressed as per cent deviation from the average 4 hourly out-

![Graph showing % change in 4-hourly phosphate excretion](image)

Fig. 1.

![Graph showing % inhibition in 4-hourly PO₄ excretion](image)

Fig. 2.
put in the first 36 hour period, are given in Table 1. A significant difference in the degree of inhibition achieved between cases of hyperparathyroidism and the rest was observed (see Fig. 2). The maximum in normals and in nephrolithiasis presumed to be not due to hyperparathyroidism lies between 58 and 96% while in hyperparathyroidism whether adenoma or hyperplasia, it lies between 0 and 39%. There was no consistent difference in the degree of increase in phosphaturia nor in the "rebound" phenomenon in either series. In hypoparathyroidism the maximum inhibition varies between 12 and 45%.

Renal Phosphorus Threshold

The renal phosphorus threshold was estimated in 28 patients with the results shown in Fig. 3. In 17 cases of nephrolithiasis not due to hyperparathyroidism the renal phosphorus threshold ranged from 2.3 mg/100 ml to 5.4 mg/100 ml and in the two cases of hypoparathyroidism on whom this procedure was carried out threshold values of 5.1 mg/100 ml and 7.2 mg/100 ml were obtained. Following 200 U.S.P. units of Parathormone threshold values of 2.45, 2.8 and 2.9 mg/100 ml were found. Appreciable overlap between normals and normals in the 2.0 to 3.0 mg/100 ml range was found.

DISCUSSION

Calcium Suppression Test

With suitable modification Howard's concept (Howard et al. 1952) of suppression of parathyroid function by a calcium infusion has been used by Kyle et al. (1962), Pronove & Bartter (1961) and Goldsmith et al. (1962). Moore &
Smith (1963) who used 12-hourly collection periods like Pronove & Bartter (1961) failed to confirm the latters' results. Using our data with 12 hourly fractions we would be unable to differentiate consistently hyperparathyroidism from control subjects. The diagnostic response in the rapid calcium infusion test of Goldsmith et al. (1962) is the failure of the initial phosphaturic effect of a calcium infusion to take place in hyperparathyroidism. From Table 1 it can be seen that this initial phosphaturic effect is in itself a variable feature and may fail to occur in normal subjects while it may occur in hyperparathyroidism. Kyle et al. (1962) have shown that bed-rest tends to diminish this response, an observation which was confirmed in one patient.

The significant drop in phosphate clearance at 8–10 hours after a calcium infusion which normally occurs failed to take place in the seven hyperparathyroid patients reported by Kyle et al. (1962). All their patients were hypercalcaemic. In our series the pattern of phosphate excretion was followed for 36 hours following the calcium infusion. This procedure, although more tedious, offers some advantages. The time of maximum inhibition in the control series and in those with nephrolithiasis, although usually occurring at the 12–16 hour collection period, is occasionally delayed (see Table 1) until 16 to 20 hours or in two cases until 20–24 hours. A doubtful suppressive action of hypercalcaemia is therefore confirmed with a more prolonged follow up. The variable hyperphosphataemic effect of a calcium infusion on the estimations of phosphate clearance is excluded in this test. The occurrence of a marked initial hyperphosphaturic effect and of a subsequent »rebound« increase, although not consistent, affords valuable contributory evidence of a normal response. It is significant that in three of the patients ultimately proven to have hyperparathyroidism the serum calcium was below 11.8 mg/100 ml and in one patient was 10.3 mg/100 ml (see Table 1). Thus the calcium suppression test under suitably controlled conditions appears worthy of trial in the more rapid diagnosis of hyperparathyroidism.

**Renal Phosphorus Threshold**

Renal phosphorus threshold values below 2.0 mg/100 ml were found in all cases of hyperparathyroidism investigated by McSwiney (1961). In this series figures above 3.0 mg/100 ml were not found in hyperparathyroidism; also figures below 2.0 ml/100 ml were not found in normal controls. However, figures between 2.0 and 3.0 mg/100 ml were found in four non-hyperparathyroid and in three hyperparathyroid subjects. Under the influence of 200 U.S.P. units Parathormone the renal phosphorus threshold varied from 2.5 to 2.9 mg/100 ml. It appears therefore, that there is an overlap between normal controls and hyperparathyroidism in the range 2.5 to 2.9 mg/100 ml. This diminishes appreciably the value of this procedure as a screening test in the investigation of renal calculi and it has been discontinued in this clinic.
Although calcium suppression and renal phosphorus threshold measure different facets of phosphorus metabolism a significant correlation between them could reasonably be expected if they were to be of equal value in the diagnosis of hyperparathyroidism. No such correlation could be demonstrated (see Fig. 4. $r^2 = 0.54$).

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