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SERUM CALCIUM HOMEOSTASIS IN RADIOIODINE TREATED THYROTOXIC SUBJECTS AS MEASURED BY ETHYLENEDIAMINE TETRA-ACETATE INFUSION

By

R. E. Goldsmith, L. R. King, E. Zalme and G. K. Bahr

ABSTRACT

Seventy four subjects treated for thyrotoxicosis with radioactive iodine ([131]I) were studied by means of an ethylenediamine tetra-acetate (EDTA) infusion such as was described by Kaiser & Pensold (1959). The response of these patients to a standard hypocalcaemic insult was followed by means of serum calcium, and in some instances serum inorganic phosphorus, analyses. The treated subjects were separated into euthyroid, hypothyroid and hypothyroid-treated-with-replacement-thyroid-medication groups. These groups were compared to a fourth group of 29 normal subjects. The results suggest that impairment of calcium mobilization was present in the irradiated subjects. However, most of the impairment could be correlated with the presence of hypothyroidism, and no loss of parathyroid reserve seemed indicated by the data.

In a previous paper it was shown that thyroidectomized euthyroid goiter patients demonstrated abnormal ethylenediamine tetra-acetate (EDTA) responsiveness when compared to normal subjects, to goitrous but unoperated subjects and to subjects undergoing herniorrhaphy (King et al. 1965). It was also shown that this abnormal EDTA responsiveness resembled that seen in subjects with typical postoperative hypoparathyroidism. A tentative conclusion, in agreement with conclusions expressed by others (Kaiser & Pensold 1959; 

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Smith et al. 1960; Wade 1960), was that thyroidectomy interfered with parathyroid reserve function although other factors were not excluded as important in the production of these results. The next obvious question was, is the same apparent compromise of parathyroid function an accompaniment of radioiodine treatment, as has been suggested by Harden et al. (1963) and Adams & Chalmers (1965). The need to evaluate the possible damaging effects of thyroid irradiation on parathyroid glands is self-evident. Since radioiodine therapy is seldom used in the treatment of nonmalignant thyroid disease associated with the euthyroid state, only subjects treated with radioiodine for thyrotoxicosis were available. Comparable groups of untreated thyrotoxic and of subtotally thyroidectomized, previously thyrotoxic, patients were not available for study. Therefore, the data currently collected were compared to the control subjects reported in the previous communication.

METHODS

The EDTA infusion and the chemical analyses were performed as noted in an earlier publication (King et al. 1965). As a matter of interest a number of samples of serum were analyzed at varying concentrations of hydrogen ion in order to plot concentration of total precipitable calcium (free, protein-bound and EDTA-bound) as well as available calcium concentration (free and protein-bound) (Toribara & Koval 1961). In all samples so analyzed the plot of total values described a rising curve of calcium concentration with a 1–2 mg per 100 ml of serum increase usually noted soon after the EDTA infusion. No significance could be attached to these total values and there were no differences not already apparent when the available calcium data were examined. Therefore, the total calcium determinations were discontinued and the results of those carried out were omitted. In the current group of tests the EDTA solution was diluted with 500 ml of 5% glucose and water and 15–20 ml of 2% procaine in order to minimize venospasm and its associated pain. Some of the serum samples were analyzed for inorganic phosphorus in addition to calcium; the method of Fiske & Subbarow (1960) was employed.

The patients in this study represent 74 previously thyrotoxic subjects treated with radioiodine and studied when euthyroid (43 subjects), when hypothyroid (19 subjects) and when euthyroid on oral desiccated thyroid after having demonstrated post-radioiodine hypothyroidism (12 subjects). The basis for selection was that radioiodine had been the sole therapeutic agent, that the subject was willing to undergo the infusion test, that the subject had no clinical evidence of parathyroid or renal disease, that the subject had normal values for serum calcium and phosphorus content and that the subject was a reasonable candidate for multiple blood sampling. One of these subjects was studied when hypothyroid and again when euthyroid on replacement therapy. Two subjects with primary myxoedema of unknown cause and 3 additional thyrotoxic subjects were treated first with thyroidectomy, and later with radioiodine for recurring or continuing Graves' disease were also studied, bringing the total number

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* Saline was used as the diluent in studies wherein serum phosphorus determinations were performed.
of subjects to 79. The original diagnosis among the 74 subjects were multinodular goiter with thyrotoxicosis (20 subjects) and anodular goiter with thyrotoxicosis, or Graves' disease (54 subjects). Total dosage with radioiodine was less than 10 millicuries in 29 and 10 or more millicuries in 45 subjects. The normal or control subjects are the 29 subjects comprising groups 1–3 of the previous publication (King et al. 1965).

All statistical treatment of data was performed according to standard methods and differences between means for normal subjects and the paired treatment group were evaluated with the Student's $t$ test since the data followed a normal distribution (Dixon & Massey 1957). In an appendix is the statistical summary of all EDTA testing performed in this laboratory for any reason.

**RESULTS**

The results of calcium analyses for each individual patient study are summarized in Tables 1 and 2 where the data are presented as means and standard errors for various groups of subjects. In Tables 1 and 2 the patients are listed according to clinical status at the time of EDTA study. The actual serum calcium values are noted in Table 1 while the data are shown in Table 2 as deviations from the control value. The data in Table 1 present difficulties for

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**Table 1.**

EDTA Infusion Studies in Radioiodine Treated Subjects: Serum Calcium Values.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Pre.</th>
<th>Post EDTA Serum Calcium, mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post. 4 h 12 h 24 h</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>43</td>
<td>Mean</td>
<td>10.01 7.73 8.84 9.54 9.90</td>
</tr>
<tr>
<td>(Euthyroid)</td>
<td>S.E.</td>
<td>0.11</td>
<td>0.13 0.12 0.12 0.13</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>19</td>
<td>Mean</td>
<td>10.21 7.68 8.75 9.35 9.75</td>
</tr>
<tr>
<td>(Hypothyroid)</td>
<td>S.E.</td>
<td>0.16</td>
<td>0.22 0.19 0.17 0.22</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>12</td>
<td>Mean</td>
<td>10.15 7.51 8.99 9.48 10.07</td>
</tr>
<tr>
<td>(On Thyroid)</td>
<td>S.E.</td>
<td>0.19</td>
<td>0.17 0.14 0.17 0.15</td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td>Mean</td>
<td>10.35 7.82 9.41 10.14 10.28</td>
</tr>
<tr>
<td></td>
<td>S.E.</td>
<td>0.08</td>
<td>.09 .07 .09 .09</td>
</tr>
</tbody>
</table>

Pre: Immediately preceding infusion.
Post: Immediately following infusion; other time are hours after end of infusion.
S.E. Standard error of the mean.
Table 2.
EDTA Infusion Studies in Radioiodine Treated Subjects: Change in Serum Calcium Values.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Post EDTA Changes In Serum Calcium, mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Post.</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>43</td>
<td>Mean</td>
</tr>
<tr>
<td>(Euthyroid)</td>
<td></td>
<td>S. E.</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>19</td>
<td>Mean</td>
</tr>
<tr>
<td>(Hypothyroid)</td>
<td></td>
<td>S. E.</td>
</tr>
<tr>
<td>Radioiodine Treatment</td>
<td>12</td>
<td>Mean</td>
</tr>
<tr>
<td>(On Thyroid)</td>
<td></td>
<td>S. E.</td>
</tr>
<tr>
<td>Normal</td>
<td>29</td>
<td>Mean</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S. E.</td>
</tr>
</tbody>
</table>

Different from normal value for that time

* P < 0.05
** P < 0.01
*** P < 0.001

comparison since the pre-infusion values for calcium concentration were lower in the radioiodine treated euthyroid subjects than in the normals with »P« value of <.05. Therefore, statistical comparisons are only reported for the data in Table 2. The significance of differences noted were also found when the data were expressed as per cent of control value. The mean value for each treatment group was compared to the mean value for the normal group for the same time interval. The »P« value was noted when the difference between that treatment group and the normals was significant at the 5% confidence level or less. Individual curves for each study have been plotted by groups and visual inspection showed that there was considerably more variation in the form of the curves in the three treatment groups than there was in the normal group; these have not been included in any figures except as group means.

The radioiodine treated, previously thyrotoxic* but currently euthyroid* patients revealed normal immediate EDTA responsiveness: that is, the fall in

* The basis for each of these clinical statements appears in the Appendix.

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serum calcium was normal at the end of the infusion, as it was in all groups. However, the return of serum calcium values to initial levels was less rapid than normal for at least 12 hours, after which it became more rapid than normal; repletion of the serum calcium concentration was normal by the 24th post-infusion hour. Radioiodine treated, previously thyrotoxic but currently hypothyroid* patients recovered from the initial hypocalcaemia in an inadequate manner demonstrating lower serum calcium concentration than did controls at intervals of 4, 12, and, unlike the previous group, also at 24 hours following the end of the infusion. Whereas, the euthyroid treated subjects were indistinguishable from the controls by the end of the period of study, hypothyroid subjects were more abnormal at that interval than at any earlier one. The mean values for these subjects deviated further from normal at each time tested than did the euthyroid treated subjects although such differences were hidden by the relatively small size of the hypothyroid group. Patients maintained in a euthyroid state with desiccated thyroid after having been made hypothyroid were different from normal only at the 12 hour post-infusion interval.

The time course of serum calcium values for all subjects is represented in Fig. 1: the data for control subjects taken from the study referred to earlier (King et al. 1965) have been plotted in Fig. 1 as the mean values and their standard error to facilitate comparison. The results of the EDTA test in the 2 subjects with untreated, idiopathic primary hypothyroidism, the radioiodine-treated subject studied when euthyroid and again later when hypothyroid and in the 3 subjects treated with surgery and, subsequently, radioiodine for the control of stubborn Graves' disease are listed in Fig. 2. The latter 3 subjects were euthyroid when studied. The subjects with idiopathic loss of thyroid function demonstrated abnormal curves with 7 of 8 values well below normal. Two of the 3 subjects treated by a combination of 2 modes of partial thyroid ablation demonstrated abnormal curves at all time intervals. The subject serving as his own control (euthyroid vs. hypothyroid) demonstrated similar results in the two studies; values for his determinations are noted in the Appendix.

The results were analyzed to see if there were correlations between diagnosis or total radioiodine dosage on the one hand and EDTA and hypocalcaemia responsiveness on the other. There was no evidence that Graves' disease and toxic nodular goiter subjects responded differently or that increasing total radioiodine dosage altered the responsiveness of the subjects to EDTA infusion.

The serum phosphorus content was determined along with the calcium content in 31 studies. These results are listed in Table 3. Statistical analysis was performed for the pre- and post-infusion values: no phosphorus results for control subjects were available. The range of values at each time interval

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Fig. 1.
The mean response of the various treated groups to EDTA-induced hypocalcaemia is compared to the mean response for 29 normal subjects. The time intervals of sampling are identical in all patients; in order to avoid confusion as the result of multiple points falling together the points of the treated groups are slightly off from the actual time of sampling which is given by the normals. Similarly, some of the standard error brackets are left out to avoid confusion with superimposed lines.

within the two groups studied was much greater than was the case with calcium. The values fell quickly from the starting value in euthyroid radioiodine treated subjects and returned most of the way to the starting value by the 12th post-infusion hour to fall again by the 24th hour. No similar return to the starting values was noted in the hypothyroid subjects, although only the post-infusion value wasa significantly depressed. The initial fall in serum phosphorus content observed in each group was similar; while the later values appeared to be higher in the euthyroid group, the differences were never significant.

**DISCUSSION**

The calcium data suggest that the response to hypocalcaemia, as measured by an EDTA test of the type herein employed, is impaired in subjects made hypothyroid by radioiodine treatment. The finding of abnormal response curves
Fig. 2.
The response of individual patients to EDTA-induced hypocalcaemia is compared to the mean response of 29 normal subjects. The same statement regarding sampling time as was made in the legend for Fig. 1 is true for Fig. 2.

Table 3.
EDTA Infusion Studies in Radioiodine Treated Subjects: Serum Phosphorus Values.

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Pre.</th>
<th>Post EDTA Serum Phosphorus, mg/100 ml</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Post.</td>
</tr>
<tr>
<td>Radioiodine</td>
<td>21</td>
<td>Mean</td>
<td>3.49</td>
</tr>
<tr>
<td>Treatment (Euthyroid)</td>
<td></td>
<td>S. E.</td>
<td>.09</td>
</tr>
<tr>
<td>Radioiodine</td>
<td>10</td>
<td>Mean</td>
<td>3.72</td>
</tr>
<tr>
<td>Treatment (Hypothyroid)</td>
<td></td>
<td>S. E.</td>
<td>.22</td>
</tr>
</tbody>
</table>

Different from Pre value of same group
* 0.025 < P < 0.05
** .01 < P < .025
*** P < .001

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in spontaneous hypothyroidism and of almost normal curves in 12 subjects previously rendered hypothyroid by irradiation and restored to a euthyroid state with desiccated thyroid are consistent with this interpretation and indicate that radiation damage to parathyroid tissue is not necessarily the factor producing abnormal results. Irradiated subjects remaining euthyroid demonstrated an equivocal response.

This subnormal response in hypothyroid subjects may reflect the absence of the salutary effect on calcium mobilization which follows administration of thyroid to hypothyroid subjects, as was first demonstrated in reports by Aub et al. (1932) and Cope & Donaldson (1937). Since an increase was noted in the absence of parathyroid tissue the mechanism is probably independent of parathyroid function. More recent work tends to confirm that thyroid hormone increases calcium mobilization independent of parathyroid hormone (Adams et al. 1965; Lukens-Meyer et al. 1965; Lukert & Meek 1965). The role of thyrocalcitonin in the production of current results is not known. Removal of the supply of this material should improve the response of the subject to hypocalcaemia since the action of thyrocalcitonin is to depress the concentration of serum calcium (Copp et al. 1962). Therefore, hypocalcaemia unresponsiveness should be ameliorated by thyrocalcitonin absence, if affected at all. The importance of changes in glomerular filtration rate, often seen in association with hypothyroidism, as a factor in producing altered hypocalcaemia responsiveness is problematic. The GFR may fall in hypothyroid subjects and improve after replacement with thyroid by mouth (Corcoran & Page 1947). However, a slowed clearance of EDTA from blood may not affect the hypocalcaemia since the action of thyrocalcitonin is to depress the concentration chelating agent and calcium which cannot be exceeded regardless of exposure time of the substances to each other (Toribara & Koval 1961); and experience has demonstrated that rapid infusion of the chelating agent is necessary to lower the serum calcium concentration at all. It is very unlikely that any moderate reduction in GFR such as would still be associated with a normal BUN value, would alter EDTA kinetics enough to produce the results in the hypothyroid subjects.

The single abnormal mean value seen in the irradiated, previously hypothyroid but currently repleted subjects at 12 hours after infusion could be related to some nonthyroidal factor which is operative in rendering this group of subjects slightly abnormal. However, these data have been statistically analyzed, together with similar data obtained on other subjects, by analysis of variance and by a modified t test on the slopes. Such analyses were carried out in order to try to resolve the significance of single point differences and to compare all the groups studied, over approximately 5 years, with each other. This should make the statistical analysis more meaningful. The results of the comprehensive statistical treatment of the data from all subjects appear
in the Appendix. The conclusion is that the subjects made hypothyroid and repleted with desiccated thyroid do not differ in any significant way from normal control subjects.

The occasional abnormal curve seen when the individual values were plotted for the irradiated, euthyroid group (not graphed herein) can well reflect inclusion of some subjects with early, and as yet unrecognized, hypothyroidism in the euthyroid group. Such interpretation is strengthened by the absence of a direct relationship between the response to EDTA infusion and total dose of administered radioiodine. It is well known that radioiodine-treated thyrotoxic subjects may develop hypothyroidism very gradually, to only partial degree and often with very little clinical evidence for the first months or years (Werner et al. 1957; Nofal et al. 1966; Goldsmith, unpubl. results). An error in clinical evaluation could readily occur and hypothyroid subjects could be called euthyroid. According to analysis of variance and a t test on the slopes the euthyroid irradiated subjects showed normal results.

The results of Adams & Charmers (1965) are not necessarily at variance with the present ones. They noted more hypothyroid subjects with serum calcium values in the low normal range than was found in controls and they found a poor EDTA response test in 7 radioiodine-treated subjects, of whom 4 were previously known to have been hypothyroid. Both they and Harden et al. (1963) suggested that hypoparathyroidism of some degree was present in irradiated thyroid subjects: the present report is at variance with this conclusion.

The theory behind the current test suggests that the EDTA-induced hypocalcaemia stimulates parathyroid hormone secretion and rapid repletion of the hypocalcaemia followed by a decreasing output of the hormone (Kaiser & Pensold 1959). Confirmation of this hypothesis has recently been offered by Aubach & Potts (1967) who noted an increase in plasma immunoassayable parathyroid hormone associated with EDTA-induced serum calcium fall and a decrease in plasma hormone content following a calcium infusion-induced return of blood calcium concentration to initial levels. Many other factors are assumed involved in this interplay but these authors only followed one. Reasoning from this theory the serum phosphorus concentration would be expected to fall some time after the induction of hypocalcaemia and its associated increase in hormone output. The serum phosphorus would be expected to rise subsequently as the rate of parathyroid hormone secretion fell. The time lag involved would be difficult to predict and renal, as well as other factors, would affect this as would the direct interplay between serum calcium and phosphorus (Greenwald 1926; Logan 1940). An insufficient outpouring of hormone in response to the induced hypocalcaemia might lead to a subnormal parathyroid-induced fall in the serum phosphorus value together with a tendency for serum phosphorus values to rise in direct response to
hypocalcaemia. The time course of the serum phosphorus concentration following EDTA infusion has been discussed by Sanderson et al. (1960), Kalliomaki et al. (1961), Estep et al. (1965) and Rosenbaum (1965, 1966).

The previous conclusion reached with EDTA studies involving thyroidectomy subjects, namely that operation was associated with some degree of hypoparathyroidism, must be reconsidered in light of the current conclusion; the possibility that factors other than parathyroid hormone secretion rate affected the EDTA test results was suggested (King et al. 1965). These factors would be the status of the skeleton, renal function, alimentation, the size of blood and soft tissue calcium pools and many other physiological considerations. These factors appeared to be normal in most of the subjects reported herein. In addition, unknown direct effects of EDTA on physiologic mechanisms must be considered (Albach 1960). The patient populations of the previous and present reports are, however, different; many of the post-thyroidectomy subjects studied with an EDTA test were originally euthyroid. There is some experience to suggest that an odd evolution of partial hypothyroidism may follow operative thyroidectomy in the toxic subject (Goldsmith, unpubl. results; Bronsky et al. 1966), just as in the irradiated thyrotoxic subject. However, a rising late incidence of hypothyroidism with inapparent clinical picture of the disability when it develops are not features known to confuse the clinician following thyroidectomy in euthyroid goiter subjects. The subjects in the earlier report were considered euthyroid at the time each was studied.

Clinically, there are only a few reports to suggest that hypoparathyroidism complicates radioiodine treatment; the first was Tighe (1952) and later ones were reviewed by Harden et al. (1963). This paucity certainly suggests that significant hypocalcaemia is a very uncommon sequela to radiation treatment for human thyrotoxicosis. The report of Freedberg et al. (1952), showing no definite pathology of parathyroid tissue in euthyroid subjects given up to 157 millicuries of $^{131}$I, is consistent with this conclusion. The report of Parrott et al. (1960) concerned rats rendered hypocalcaemic (during parturition) following $^{131}$I thyroidectomy, even when given replacement thyroxine. These animals demonstrated parathyroid damage. However, the dose used (5 millicuries per kg body weight) is well in excess of any dose used to treat human thyrotoxicosis. The current report suggests that poor mobilization of calcium accompanies hypothyroidism: radio-calcium kinetics also suggest this (Kranes et al. 1956). Whether altered mobilization reflects some nonspecific effect of thyroid hormone lack, such as decreased renal clearance of EDTA or decreased rate of bone blood flow, or some specific effect of hormone lack, such as a decrease in the rate of bone glycolysis and energy build up, can not be concluded from the present data. However, the changes are of such a magnitude as to make known nonspecific effects of thyroid hormone absence unlikely factors in the production of these results.
The complaint of extremity pains commonly seen with hypothyroidism may be a clinical consequence of such poor mobilization of calcium rather than of relative tissue anoxia. Study is needed in regard to this point since, in the experience of the authors, peripheral skeletal muscle cramping (often at rest) is one of the more reliable historical points which allows the clinician to suspect early hypothyroidism. If thyrocalcitonin production is lost along with thyroxine production as the result of radiation damage to the thyroid there would be endogenous adjustment to compensate for the effect of thyroxine absence on calcium mobilization. The answer to this is not known and the possibility of transient, local »tetany« as the cause of the aforementioned cramps warrants considerataion.

**APPENDIX**

**Statistical Summary**

It was difficult to substantiate a normal distribution for the data because of the small sample size for some groups. Accordingly, the data were first examined by the non-parametric median test. It was established that the samples were indeed drawn from different populations, except at hour 1 (the P values were < .05 for hour 4, < .005 for hour 12 and < .05 for hour 24). With heterogeneity established, the classic parametric statistical tests could be applied with the assurance of knowing that the results would not be misleading. Preliminary testing was done by Student's t test and these results are reported elsewhere (King et al. 1965; King et al., unpubl. results; present text). Each sample mean was compared to the mean of the normals for each point in time. Description of the normal control group has been published previously (King et al. 1965). Intergroup comparisons were made by analysis of variance and Hartley's sequential test for means. These tests compared the data points for each time interval as independent samples. This approach would not take into account the influence on a data point from the data points preceding it in time. To evaluate this interdependence, an average early slope was calculated for each group on the basis of the first 2 points and compared to the early slope of the normal group. If a group was different from normal by either slope analysis or analysis of variance, at a probability of < .01, it was accepted as significantly different from normal. If a group differed from the normal group by both tests with a probability of < 0.025 or < 0.05 it was also considered significantly different from normal. The results of these calculations are noted in Table 4.

**Clinical Summary**

All patients were evaluated clinically by one person (REG) at the time of infusion; however, these patients also had been seen by the same observer at least twice yearly ever since 131I therapy as part of a PHS follow-up study. In addition, each patient was subjected to a BMR study, a 131I uptake study and, in many instances, serum PBI and cholesterol determinations. Particular attention was given to the diagnosis of early, incomplete hypothyroidism. This diagnosis was made when the patient com-
Table 4. 
EDTA Infusion Test Results: Statistical Comparison of Treatment Groups to Normals

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of Patients</th>
<th>Analysis of Variance</th>
<th>Slope Values, Student’s t Test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>post 4 h 12 h 24 h</td>
<td></td>
</tr>
<tr>
<td>Operated Goiters</td>
<td>20</td>
<td>NS * * NS</td>
<td>**</td>
</tr>
<tr>
<td>Hypoparathyroid</td>
<td>5</td>
<td>NS * * *</td>
<td>** **</td>
</tr>
<tr>
<td>Radioiodine Treatment (Euthyroid)</td>
<td>43</td>
<td>NS NS NS NS</td>
<td>NS</td>
</tr>
<tr>
<td>Radioiodine Treatment (Hypothyroid)</td>
<td>19</td>
<td>NS ** NS **</td>
<td>** **</td>
</tr>
<tr>
<td>Radioiodine Treatment (On Thyroid)</td>
<td>12</td>
<td>NS NS NS NS</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperparathyroidism (Preoperative)</td>
<td>6</td>
<td>NS ** NS **</td>
<td>NS</td>
</tr>
<tr>
<td>Hyperparathyroidism (Postoperative)</td>
<td>12</td>
<td>NS ** * NS</td>
<td>*</td>
</tr>
<tr>
<td>Negative Neck (Postoperative)</td>
<td>5</td>
<td>NS NS NS NS</td>
<td>*</td>
</tr>
</tbody>
</table>

Significance of differences:
*  = .025 < P < .05  
** = P < .01  
NS = not significant

plained of or admitted to muscle cramping and/or unusual fatigue, cold intolerance, skin dryness and the like; when the BMR was < −20 %; when the 131I uptake was < 15 % at 24 h; when the serum PBI concentration was < 3.2 μg/100 ml serum; when the serum cholesterol was > 280 mg/100 ml serum; and when the physical examination was not incompatible with the diagnosis. Text-book criteria for the clinical diagnosis of hypothyroidism were seldom satisfied by these subjects. Maintenance therapy for the treated hypothyroid subjects consisted of 130–195 mg desiccated thyroid substance daily.

As noted in the text, skeletal, intestinal and renal function, among other factors, can be expected to affect calcium dynamics in a study such as that herein reported. No patient included above had clinical evidence of abnormalities in these systems. Those who had illnesses known to involve these systems, i.e. breast neoplasm, acromegaly, menopause and the like, were subjected to specific investigation to allow for assessment of the functions concerned. In no instance was there evidence of significant abnormality involving these systems.

The calcium values found in the one subject studied when euthyroid on thyroid replacement follow. Pre, 11.0; Post, 7.2; 4 h, 10.6; and 24 h, 10.9 mg/100 ml serum while hypothyroid; Pre, 9.8; Post, 8.5; 4 h, 8.6; 12 h, 8.8; and 24 h, 9.4 mg/ml serum.
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