Radioimmunoassays for Intact and Carboxyl-terminal Parathyroid Hormone: Clinical Interpretation and Diagnostic Significance

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ABSTRACT

The phenomenal growth in our knowledge of parathyroid hormone (PTH) physiology, chemistry and radioimmunoassay in the past 15 years has produced a significant increase in the use of the assay in the clinical laboratory evaluation of patients with disorders of calcium homeostasis. Recent experience with assays that have specificities for different regions of the amino acid sequence of the hormone and that can thus measure different portions of the total immunoreactivity in blood suggests that there may be different clinical applications for such assays. This report describes two different radioimmunoassay procedures and the clinical experience with each and suggests how each assay may be utilized in clinical evaluation of possible parathyroid dysfunction. The assay for carboxyl-terminal PTH is more useful in the differential diagnosis of the possible causes of hypercalcemia; the intact PTH assay is preferred in selective venous catheterization for preoperative localization of hyperfunctioning tissue, and both assays have usefulness in the evaluation of patients with hypocalcemia. In chronic renal failure, the considerations are more complex. In many patients, the intact PTH assay is preferred for monitoring the clinical course; however, in other patients the carboxyl-terminal PTH assay has been more useful. The best assay for each patient must be determined by initial evaluation with both assays.

Introduction

It is now widely agreed that measurement of parathyroid hormone (PTH) levels in serum by radioimmunoassay has become one of the most useful tools to the clinician in the diagnosis and treatment of parathyroid gland disorders. Although not always appreciated, the availability of diagnostically applicable radioimmunoassays for serum PTH has effectively changed the clinician’s approach to the evaluation of patients with suspected parathyroid gland dysfunction by allowing direct measurement of circulating levels of the hormone. Such an approach, not possible before the advent of the radioimmunoassay for PTH, has become increasingly important recently because of the greater frequency of detection of hypercalcemia as a result of the routine measurements of serum calcium obtained.
as one of the measured components with multichannel analyzers.

Berson and co-workers were the first to describe a radioimmunoassay for PTH. A large number of other assays have been described in the intervening years, and the demand for the assay continues to increase. As might be predicted, however, the clinical validation and performance standards of some assays have not been as rigorous as might be hoped. The well established fact that PTH in blood is heterogeneous has also complicated its measurement.

As a result, confusion has arisen which has led to some disenchantment with PTH radioimmunoassays, and there have even been suggestions that other tests (notably, that for nephrogenous 3',5'-cyclic adenosine monophosphate) might be better reflections of parathyroid gland function. While we would certainly agree that measurement of immunoreactive parathyroid hormone (iPTH) can be challenging in that it requires extra attention to technical details, quality control and clinical validation, our experience with the test over the past seven years in many tens of thousands of patients has confirmed its usefulness as the best single test for parathyroid dysfunction.

The two principal forms of PTH in peripheral blood are intact PTH, which is a polypeptide of 84 amino acids, and carboxyl (C)-terminal fragments of PTH, which may comprise as much as 90 percent of the total immunoreactivity in the plasma of patients with primary hyperparathyroidism. Both forms of PTH are secreted by the parathyroid glands. The precise molecular weight of the C-terminal fragments is not known; they are believed to be derived from the C-terminal region of the PTH molecule, to be formed through metabolic cleavage of intact PTH, and to be biologically inert. In general, the PTH radioimmunoassays that have been developed measure primarily either biologically active PTH or these C-terminal fragments. While many of these assays have clear diagnostic applicability by themselves, our possession of two different radioimmunoassays with widely different region specificities for PTH has allowed us to measure both of the major forms of iPTH in blood, in many cases in the same patients. Such information has increased the clinical usefulness of iPTH measurement over that which could be derived from one assay alone.

Two radioimmunoassays are described for PTH, their clinical validation and interpretation as well as their differing usefulness in evaluating various classes of patients with suspected disorders of parathyroid gland function and calcium homeostasis.

Materials and Methods

The details of the procedures for both assays have been completely described elsewhere and need not be elaborated upon here. Both assays use the same standard bovine PTH, dextran-coated charcoal preparation, and equipment such as soft glass incubation tubes, pipettors, etc. Attention will be focused here on those features which differ in the two assays.

ANTISERA

The antiserum with specificity primarily for intact PTH (identified as GP204) was prepared by immunizing a guinea pig subcutaneously with a preparation of bovine intact PTH conjugated to bovine serum albumin, followed by booster immunizations with unconjugated bovine intact PTH.

The antiserum with specificity against the C-terminal region of PTH (GP75U) was produced by intradermal immunization of a guinea pig with a preparation of C-terminal fragments of human PTH.
DILUENTS

The diluents for the two assays are different, and substituting either diluent for the other adversely affects that assay. The diluent for the intact iPTH assay consists of 0.02 M sodium barbital buffer, pH 8.6, 250 KIU per ml of Trasylol* and 2 percent normal guinea pig serum; the diluent for the C-terminal iPTH assay consists of 0.085 M sodium barbital, pH 8.6, 500 KIU per ml Trasylol, 0.1 mg per ml merthiolate, and 10 percent normal human serum.

INCUBATION PROCEDURES

Both assay procedures employ non-equilibrium incubation conditions to improve sensitivity. In the assay for intact iPTH, preincubation (without $^{125}$I-PTH) is for two days, followed by three additional days of incubation with $^{125}$I-PTH. In the assay for C-terminal iPTH, there is a three-day preincubation prior to a three-day incubation with $^{125}$I-PTH. All incubations are at 4°C in a reciprocating shaker.†

SEPARATION OF "ANTIBODY-BOUND" AND "FREE" PTH TRACERS

After addition of dextran-coated charcoal and centrifugation, the resulting charcoal pellets are saved and counted (after a wash step) for the intact iPTH assay. In the C-terminal iPTH assay, the corresponding supernates are saved and counted.

CALCULATIONS

In the intact iPTH assay, the average number of counts in the glass-binding controls is subtracted from the counts for each tube containing charcoal, since this portion of the $^{125}$I-PTH is adsorbed to glass instead of charcoal. The counts for each standard (or zero standard) tube and the average incubation damage counts are subtracted from the average total counts to obtain the values for antibody-bound counts for the standard points. The counts for all tubes containing unknown or control serum and the counts for the serum interference controls for the corresponding serum volumes are subtracted from the average total counts to obtain the values for antibody-bound counts for all of the serum tubes.

In the C-terminal iPTH assay, the values for antibody-bound counts (supernates) are directly counted rather than being computed as in the intact iPTH assay. However, these counts must be corrected for incubation damage and serum interference with the binding of $^{125}$I-PTH to charcoal as follows: the average incubation damage control counts are subtracted from the counts for each standard or zero standard tube, from the counts for serum tubes in which the serum specimen was diluted prior to assay and from the counts for all tubes containing 50 μl volumes of serum. The counts for the individual serum specimen controls containing 100 or 200 μl volumes of each serum specimen are subtracted from the count values for the corresponding tubes that also contained antiserum.

The remainder of the calculation procedure is the same for both assays. The average antibody-bound counts in the zero standards are divided by the average total counts to determine "assay binding" for each assay run. All of the antibody-bound counts for standards and unknown or control serum samples are divided by the antibody-bound counts for the zero standards and multiplied by 100 to obtain the percentage of $^{125}$I-PTH bound for each standard or serum tube. The standards are plotted by the logit procedure in which the log of the percent bound is plotted as a function of the log of the pg of standard PTH in each tube. The amount of PTH in each unknown or control serum tube is then obtained from the standard curve

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* FBA Pharmaceuticals, Div. of Mobay Chem. Corp.
† Eberbach Corp.
using the logit of the percent bound for each serum tube. This amount of PTH is then multiplied by the factor necessary to equate the volume of serum used in that tube to a 1 ml serum volume.

Performance Data

Sensitivity and Specificity

In figure 1 are shown typical standard lines for pure bovine PTH as obtained with each of the two assays. The data are plotted by the logit method.30 The lower limit of detection in the intact iPTH assay is about 75 pg Eq per ml of bovine intact PTH (95 percent of antibody-bound $^{125}$I-PTH); that for the C-terminal iPTH assay is about 150 pg Eq per ml (90 percent of antibody-bound $^{125}$I-PTH). Measurement of iPTH in many thousands of patients' sera with both assays has indicated parallelism between dilution curves of sera and the bovine intact PTH standard in all but a very few cases. This parallelism confirms the validity of using bovine PTH as the standard for each assay.

It has previously been reported by us that the two assays have widely different specificities, as assessed with pure peptide fragments of bovine PTH.22 The antiserum used for the intact iPTH assay (GP204) does not react with a fragment from the C-terminal region (53 to 84) of intact PTH, nor a fragment from the middle region (27 to 44) of intact PTH. Reactivity with a fragment from the N-terminal region (1 to 34) of intact PTH is only about 0.007 percent of the reactivity with intact PTH.20,22 In sharp contrast, antiserum GP75U, which is used in the C-terminal iPTH assay, reacts with the 53 to 84 C-terminal fragment on an equimolar basis with intact PTH; it does not recognize large excesses of either the 1 to 34 or 27 to 44 fragments.11,22

We have recently investigated further the specificity of each assay by fractionating hyperparathyroid serum by a high-resolution gel filtration procedure.12 This technique separates the forms of PTH in serum on the basis of their molecular sizes, thus permitting direct evaluation of the reactivity of each antiserum with these various forms. Based on these studies, we
have concluded that antiserum GP204 (intact iPTH assay) reacts predominantly with intact hormone and recognizes PTH fragments only weakly; antiserum GP75U (C-terminal iPTH assay), on the other hand, is directed virtually exclusively toward the C-terminal region of PTH.12

**PRECISION**

Quality control of the iPTH assays has been assessed through the routine use of three different pools of normal and hyperparathyroid serum in every assay run. Over the past seven years, the inter-assay coefficients of variation have consistently been 7 to 12 percent for these serum pools in the intact iPTH assay.20 The C-terminal iPTH assay, which is more recent in origin, has shown similar coefficients of variation for the same serum pools.

**Results in Normal Subjects and Patients**

**INTACT iPTH**

As previously reported, the mean intact iPTH (± S.D.) in 93 normal subjects was 255 (± 46) pg Eq per ml based on the bovine PTH standard.20 The normal range (mean ± 2 S.D.) was 163 to 347 pg Eq per ml. The assay for intact iPTH described here has demonstrated an inverse relationship between iPTH and serum calcium levels in normal subjects,20 in a manner similar to that first described by Arnaud and associates.3 As shown in figure 2, a plot of intact iPTH versus calcium has shown a highly significant negative correlation (r = −0.412, p < 0.001); parallel lines that are 2 S.D. above and below the regression line encompass all but one of the normal points. These parallel lines are therefore considered to be the normal limits.

In 412 patients with primary hyperparathyroidism confirmed by surgical removal of hyperfunctioning parathyroid tissue, intact iPTH ranged from 155 to 5363 pg Eq per ml, but only 228 (55.3 percent) had values greater than 347 pg Eq per ml. However, as first demonstrated by Arnaud et al3 and later with this assay,7,20 the apparently normal iPTH levels in hyperparathyroid patients are, in fact, inappropriately high for their corresponding serum calcium values. Thus, by plotting intact iPTH as a function of serum calcium (figure 2), 398 (97 percent) of the 412 points for patients with primary hyperparathyroidism are separated from the normal limits and from points for patients with hypercalcemia not due to parathyroid hormone. If, as shown in figure 2, one assay C.V. is added to the highest point (206 pg Eq per ml) for a non-hyperparathyroid hypercalcemic patient in order to provide greater statistical significance to differentiation of the primary hyperparathyroid results, 382 (93 percent) of the results are found to be higher than that value of 225 pg Eq per ml.

The group of 30 patients with hypercalcemia not due to parathyroid disease consisted of seven with multiple myeloma, five with milk alkali syndrome, three with hypervitaminosis D, three with Paget’s disease of bone, two with sarcoidosis and 10 with various cancers and bony metastases and no evidence of ectopic secretion of PTH. Intact iPTH values in this group ranged from 71 to 206 pg Eq per ml.

In contrast to the primary hyperparathyroid patients, a group of 119 hypercalcemic patients with malignancy thought to have ectopic production of parathyroid hormone had intact iPTH values that were generally lower even though their serum calcium values were generally higher. In this group, intact PTH ranged from 142 to 876 pg Eq per ml. Only 22 (18.5 percent) had values greater than 347 pg Eq per ml, but 82 (69 percent) had values that could be considered inappropriately high for their corresponding serum calcium values. Thus, many of these patients overlap with the primary hyperparathyroid patients, even though as a group they tend to have lower intact iPTH values.

In 160 patients with secondary hyperparathyroidism owing to chronic renal
Figure 2. Serum intact iPTH concentration (pg Eq per ml) as a function of serum calcium concentration (mg per dl) in normal subjects (•), patients with surgically proven primary hyperparathyroidism (♦), patients with hyperparathyroidism not due to hyperparathyroidism (◼), patients with chronic renal failure and probable secondary hyperparathyroidism (●), and patients with idiopathic or surgical hypoparathyroidism (○). The mean iPTH value in the normal subjects was 255 pg Eq per ml and the S.D. was 46 pg Eq per ml. The solid diagonal line was determined by regression analysis of the normal points (r = -0.412, p < 0.001). The dashed lines are parallel to and 2 S.D. above and below the regression line. The dotted line is an extension of the upper dashed line to a serum calcium of 11.1 mg per dl and thence parallel to the abscissa at an iPTH value of 225 pg Eq per ml which is one C.V. (9.5 percent) above the highest point (206 pg Eq per ml) for a patient with hypercalcemia not due to hyperparathyroidism. The solid bar indicates the normal range for serum calcium. (Figure is reproduced from reference 20 which was published in this journal.)

failure, intact iPTH ranged from 231 to 9151 pg Eq per ml; 137 (86 percent) had intact iPTH levels greater than 347 pg Eq per ml.

A group of 40 patients with idiopathic or surgical hypoparathyroidism had intact iPTH values ranging from non-detectable (about 75 pg Eq per ml) to 281 pg Eq per ml. However, just as the values for patients with primary hyperparathyroidism are inappropriately high for their elevated serum calcium levels, 37 (93 percent) of these hypoparathyroid patients had intact iPTH values that were inappropriately low for their subnormal serum calcium levels.

The plot of intact iPTH versus serum calcium is highly effective in differentiating primary hyperparathyroidism from normal subjects and from other causes of hypercalcemia, and also in identifying patients with surgical or idiopathic hypoparathyroidism or chronic renal failure and secondary hyperparathyroidism. However, use of the plot requires a knowledge of the precision of both the intact iPTH and serum calcium tests, an understanding of the inverse relationship between intact iPTH and serum calcium, and study of the published clinical experience with the assay. In order to reduce the need for these considerations, Hawker et al.21 have described the application of a bivariate classification analysis which was able to estimate the probability that a result from a given patient should be interpreted as belonging in each of the
Figure 3. Serum C-terminal iPTH concentration (pg Eq per ml) as a function of serum calcium concentration (mg per dl) in normal subjects (○), patients with surgically proven primary hyperparathyroidism (●), patients with malignancy and hypercalcemia (□), patients with chronic renal failure and probable secondary hyperparathyroidism (■), and patients with surgical hypoparathyroidism (○). The shaded area identifies the nondetectable zone of the assay which is up to 150 pg Eq per ml.

five separate areas (normal iPTH with normal calcium, high iPTH with low calcium). This procedure was found to have an overall accuracy of 90 percent of actual diagnoses which were correctly predicted, as defined by correlation of the
highest estimated probability with the actual diagnosis.

**C-Terminal iPTH**

In figure 3 are shown C-terminal iPTH values plotted as a function of serum calcium for 183 normal subjects and patients with various disorders. The mean iPTH value (± S.D.) in the group of normal subjects was 256 (± 59.5) pg Eq per ml, and the mean ± S.D. range was 137 to 375 pg Eq per ml. Since the lower limit of detection in this assay is considered to be 150 pg Eq per ml, the normal range is expressed as < 150 to 375 pg Eq per ml. Only 7 (4 percent) of the normal subjects had C-terminal iPTH levels below 150 pg Eq per ml. There was no statistically significant correlation between C-terminal iPTH and calcium levels in this group of normal subjects.

The close similarity in the normal ranges obtained with the two assays (intact iPTH and C-terminal iPTH), even though two separate groups of normal subjects were analyzed, suggests that normal subjects have predominantly intact iPTH in their circulation, because both antisera are known to be cross-reactive with intact PTH. Definitive support for this suggestion, however, must await study of serum from normal individuals fractionated by high resolution gel filtration in order to identify the molecular species of PTH present.

A group of 109 patients with surgically confirmed primary hyperparathyroidism had C-terminal iPTH values ranging from 295 to 27,000 pg Eq per ml. All but six (5.5 percent) had values greater than 375 pg Eq per ml, and there was a strong positive correlation between C-terminal iPTH and calcium levels ($r = 0.258$, $p < 0.01$).

In 33 hypercalcemic patients with various malignancies suspected to be producing PTH ectopically, C-terminal iPTH levels ranged from < 150 (nondetectable) to 893 pg Eq per ml. Three patients (9 percent) had values less than 150 pg Eq per ml, and 21 others (64 percent) had values within normal limits. Only nine patients (27 percent) had values exceeding 375 pg Eq per ml. The range of values for C-terminal iPTH in these patients is clearly much lower than the range of values for C-terminal iPTH in patients with surgically proven primary hyperparathyroidism even though their serum calcium values are just as high. It is of great interest that a separate group of 119 hypercalcemic patients with malignancy had a nearly identical range of 142 to 876 pg Eq per ml when measured in the intact iPTH assay. These findings, and the observation that patients with primary hyperparathyroidism have predominantly C-terminal fragments in their circulation, suggest that hypercalcemic patients with malignancy thought to have ectopic production of PTH may have predominantly intact PTH in their circulation. However, just as is true for normal subjects, this hypothesis will require confirmation by fractionation of serum specimens from these patients on high resolution gel filtration columns.

In a group of 67 patients with chronic renal failure and probable secondary hyperparathyroidism, all patients had values greater than 375 pg Eq per ml, the range being 560 to 145,000 pg Eq per ml. These results are consistent with reported findings for other assays with C-terminal specificity and are undoubtedly explained by the now well-known observation that adequate renal function is required in order for C-terminal iPTH fragments to be cleared from the circulation. In fact, it has been estimated that as much as 80 percent of the C-terminal iPTH measured in the blood of a patient with chronic renal failure represents accumulated C-terminal fragments while only 20 percent of the value can be attributed to recent gland activity.

Of 14 patients with surgical hypoparathyroidism, 13 (93 percent) had non-
detectable C-terminal iPTH levels, while one patient was found to have an apparently normal value.

**DISCUSSION AND CLINICAL INTERPRETATION**

The past several years have witnessed a great increase in our knowledge of PTH metabolism and the different molecular forms of PTH in blood. It is now apparent that the principal forms of circulating PTH are the intact hormone and C-terminal PTH fragments.\(^2\) It has also become clear that measurements of these two PTH forms have different utilities in the diagnosis of parathyroid dysfunction and disorders of mineral homeostasis.\(^2,3\) Thus, measurement of intact (biologically-active) PTH best reflects PTH secretion and can give information about acute changes in this secretion in response to hyper- or hypocalcemic stimuli. Measurement of C-terminal PTH fragments, on the other hand, best reflects steady-state levels of PTH and has been shown to be more useful in identifying states of chronic parathyroid hyperfunction.\(^2\) With these general guidelines in mind, the clinician can select the PTH assay best suited to the particular diagnostic situation.

There is an additional factor to consider. The metabolism of intact PTH to its fragments and the clearances of intact PTH and its fragments from the circulation vary considerably among patients,—even those with the same diagnosis.\(^2\) Both intact and C-terminal iPTH have been measured by us in 45 patients with surgically proven primary hyperparathyroidism. In figure 4 is a frequency distribution of the percentage of the total iPTH (sum of the two assay results) which is the C-terminal iPTH component for these 45 patients. The figure shows that the percentage of C-terminal iPTH varies from 40 percent to greater than 95 percent, and that most of the patients had between 60 to 90 percent of their total iPTH represented by the C-terminal iPTH result, in agreement with earlier estimates based on gel filtration findings.\(^4,9\) One obvious contributing factor to this variation is that a significant number of patients with primary hyperparathyroidism have renal impairment.\(^25,3\) When coupled with the previously mentioned observations that adequate renal function is required for clearance of C-terminal fragments,\(^19,3\) it is evident that primary hyperparathyroid patients with renal impairment will tend to have higher percentages of total iPTH in the form of C-terminal fragments.

In figure 5 is a plot of the C-terminal iPTH results as a function of the intact iPTH results for the 45 patients with surgically proven primary hyperparathyroidism discussed previously. The shaded zones are the normal ranges for the respective tests. All but 3 (6.7 percent) of the patients had elevated C-terminal iPTH values. In contrast, only 19 of the patients had intact iPTH values greater than 2 S.D. above the mean of the normal group, but another 13 had intact iPTH values inap-
appropriately high for serum calcium with greater than 90 percent probability. This made a total of 32 (71 percent) that were correctly diagnosed with confidence by the intact iPTH assay, showing the superiority of the C-terminal assay as a single test for primary hyperparathyroidism.

However, when the specimens for the three patients with normal C-terminal iPTH levels were tested for intact iPTH, one was found to have a markedly elevated value and the other two had values that were inappropriately elevated for their corresponding serum calcium levels with 99 percent or greater probability. Thus, all 45 patients were correctly differentiated by using the C-terminal iPTH assay first, followed by the intact iPTH assay in the equivocal cases. Although the total number of patients evaluated to date is small, the data suggest that the use of two assays with markedly differing specificities has a greater overall effectiveness than either assay alone in the diagnosis of primary hyperparathyroidism.

The diagnosis of primary hyperparathyroidism is frequently concerned with the differentiation of that disorder from other causes of hypercalcemia. Of these, the most common is hypercalcemia associated with various nonendocrine malignancies without bony metastases.
(frequently called pseudohyperparathyroidism or ectopic hyperparathyroidism). In many instances, these malignancies cause hypercalcemia by production of parathyroid hormone, but prostaglandin E and the osteoclast activating factor have also been identified as causes of the hypercalcemia in some patients.

As mentioned previously, the ranges of values for iPTH in patients with various malignancies and hypercalcemia were similar (142 to 876 pg Eq per ml for intact iPTH, < 150 to 893 for C-terminal iPTH), and the percentages of the groups of patients that had elevated values were also similar. Because the primary hyperparathyroid patients have values for C-terminal iPTH that are so much higher than the values in patients with malignancy, it is concluded by us that (1) the blood of patients with primary hyperparathyroidism contains a form of iPTH that is either not found or is found only in small quantities in ectopic hyperparathyroidism and that this form is probably a C-terminal fragment and (2) the blood of patients with ectopic hyperparathyroidism contains predominantly intact iPTH. Therefore, in accomplishing the differential diagnosis of primary versus ectopic hyperparathyroidism, the C-terminal iPTH assay should be used first because it generally has given much different values in these two situations. However, the intact iPTH assay may also be of value in distinguishing these groups.

Patients with chronic renal failure and secondary hyperparathyroidism almost always have elevated iPTH levels with both assays (86 percent elevated for intact iPTH versus 100 percent for C-terminal iPTH). The role of the PTH assay in these patients is largely one of monitoring their clinical condition over time during a program of dialysis and therapy (including renal transplantation). If the patient is clinically improved (reversal of secondary hyperparathyroidism), a decline in iPTH values should be observed. Both iPTH assays have shown such correlations in many, but not all, patients.

In clinically improved patients (not receiving a transplant) in whom C-terminal iPTH did fall, the values in no instances returned to within normal limits. Presumably, this is because lack of renal function prevented removal of the C-terminal fragments. In some situations, intact iPTH values were observed to fall when C-terminal iPTH either did not fall at all or fell only marginally. In other patients, initial intact iPTH values were within normal limits and significant declines could not be detected.

Hence, there is no single PTH assay that can be used universally in all renal failure patients. It is concluded by us that both iPTH assays could be used at the onset of a program of dialysis and therapy to establish baseline iPTH levels. Depending on these results and the results observed during treatment, one or the other assay could be selected for periodic monitoring of the patient's clinical course, with the second assay being tried if the first fails to correlate.

In hypocalcemic disorders, such as rickets, osteomalacia, vitamin D deficiency, pseudohypoparathyroidism, acute renal failure, or gastrointestinal disease (malabsorption), both iPTH assays have generally shown slightly elevated iPTH levels. In hypocalcemia, owing to either surgical or idiopathic hypoparathyroidism, the C-terminal iPTH assay has generally given nondetectable values, while the intact iPTH assay has given measurable values. However, these values have been in the lower end of the normal range or below normal and were thus inappropriately low for their serum calcium values.

The technique of selective catheterization of veins draining the neck and mediastinum to localize preoperatively hyperfunctioning parathyroid tissue has been shown to be clinically useful in some
patients, especially those who have already had unsuccessfully parathyroid exploration.\(^{15,16}\) The assay for intact iPTH has been found to be more useful for specimens collected by this procedure, presumably because this assay measures primarily the secreted form of iPTH and is less able to recognize the C-terminal iPTH fragments in venous blood than the C-terminal assay.

This latter point is important, since there is peripheral conversion of intact iPTH to C-terminal fragments and the background or baseline C-terminal iPTH values have tended to run higher making the increased levels of C-terminal iPTH in catheterized veins harder to detect. In direct comparisons of the two assays in numerous catheterization series, the iPTH values obtained with the intact iPTH assay have more clearly indicated the exact source of increased PTH appearing in peripheral blood.\(^{12}\) These findings are in the agreement with the report of Reiss et al\(^{29}\) who demonstrated the advantages of an amino-terminal specific anti-

### References


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